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WO 97/28141
PCT/FR97/00203

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

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FRANCE

[illegible stamp]

Date of mailing (*day/month/year*)	
07 August 1997 (07.08.97)	
Applicant's or agent's file reference	IMPORTANT NOTICE
338 198	

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/FR97/002023	03 February 1997 (03.02.97)	02 February 1996 (02.02.96)

Applicant

PIERRE FABRE MEDICAMENT etc

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
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If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

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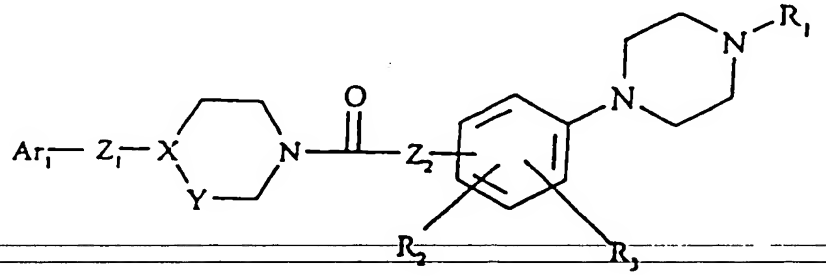
(54) Title: NOVEL AROMATIC PIPERAZINES DERIVED FROM SUBSTITUTED CYCLOAZANES, METHOD FOR PREPARING SAME, PHARMACEUTICAL COMPOSITIONS, AND USE THEREOF AS DRUGS

(54) Titre: NOUVELLES PIPERAZINES AROMATIQUES DERIVEES DE CYCLOAZANES SUBSTITUES, AINSI QUE LEUR PROCEDE DE PREPARATION, LES COMPOSITIONS PHARMACEUTIQUES ET LEUR UTILISATION COMME MEDICAMENTS



(I)

(57) Abstract

Compounds of formula (I), wherein R_1 is hydrogen or straight or branched C_{1-6} alkyl, Z_2 is O, NH, CH_2O or CH_2NH, each of R_2 and R_3, which are the same or different, is hydrogen or a group selected from straight or branched alkyl, alkoxy, thioether, nitrile, trifluoromethyl or halogen (F, Cl, Br, I), or, when they are adjacent, R_2 and R_3, taken together, form a 5- or 6-membered ring in order to form, e.g., naphthyl, tetrahydronaphthyl, benzopyrane or benzodioxane, X-Y is NCH_2, CH-CH_2, C=CH, N or NCH_2CH_2, and Z_1 is -$(CH_2)_m$, -$(CH_2)_n$CO-, -CO-, -$CO(CH_2)_n$-, -SO_2-, -$SO_2(CH_2)_n$-, -$O(CH_2)_n$-, -$O(CH_2)_nCO$-, -OCO-, -$NH(CH_2)_n$-, -$NH(CH_2)_nCO$-, -NHCO-, -$NHCO(CH_2)_n$-, -$NH(CH_2)_nSO_2$-, -$NHSO_2$-, -$NHSO_2(CH_2)_n$-, -CH=CHCO-, -CCCO- -$(CH_2)_mSO_2$-, -$O(CH_2)_mSO_2$-.

(57) Abrégé

La présente invention concerne les composés de formule (I) dans laquelle: R_1 représente un hydrogène ou un alkyle linéaire c ramifié comprenant de 1 à 6 atomes de carbone, Z_2 représente O, NH, CH_2O ou CH_2NH, R_2 et R_3 identiques ou différents représente: un hydrogène ou un groupe choisi parmi un alkyle linéaire ou ramifié, un alcoxy, thioéther, nitrile, trifluorométhyle ou halogène (F, C Br, I), ou, R_2 et R_3, lorsqu'ils sont adjacents, pris ensemble, forment un cycle à 5 ou 6 chaînons de façon à constituer par exempl un naphtyle, un tétrahydronaphtyle, un benzopyrane ou un benzodioxane, X-Y représente NCH_2, $CH-CH_2$, C=CH, N ou NCH_2CH_2, Z représente $-(CH_2)_n$, $-(CH_2)_n$ CO-, -CO-, $-CO(CH_2)_n$-, $-SO_2$-, $-SO_2(CH_2)_n$-, $-O(CH_2)_n$-, $-O(CH_2)_nCO$-, -OCO-, $-NH(CH_2)_n$-, $-NH(CH_2)_nCO$ -NHCO-, $-NHCO(CH_2)_n$-, $-NH(CH_2)_nSO_2$-, $-NHSO_2$-, $-NHSO_2(CH_2)_n$-, -CH=CHCO-, -CCCO- $-(CH_2)_nSO_2$-, $-O(CH_2)_nSO_2$-.

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NOVEL AROMATIC PIPERAZINES DERIVED FROM SUBSTITUTED CYCLOAZANES, METHOD FOR PREPARING SAME, PHARMACEUTICAL COMPOSITIONS, AND USE THEREOF AS DRUGS

The present invention relates to novel aromatic piperazines derived from substituted cycloazanes, as well as the method for preparing them, pharmaceutical compositions containing them and their use as drugs.

Serotonin or 5-hydroxytryptamine (5-HT) is a neurotransmitter and a neuromodulator which is involved in numerous physiological and pathological processes. Serotonin plays an important role both at the level of the nervous system and at the level of the cardiovascular and gastrointestinal systems. At the central level, serotonin controls functions as varied as sleep, locomotion, food intake, learning and memory, endocrinal modulations, sexual behavior and thermo-regulation. In the marrow, serotonin plays an important role in the systems for controlling peripheral nociceptive afferents (cf. A. Moulignier, Rev. Neurol. (Paris), 150, 3-15, 1994).

Serotonin may also play an important role in various types of pathological conditions such as certain psychiatric disorders (anxiety, depression, aggressiveness, panic attacks, obsessive compulsive disorders, schizophrenia, suicidal tendency), certain neurodegenerative disorders (Alzheimer-type dementia, Parkinsonism, Huntington's chorea), anorexia, bulimia, alcoholism-related disorders, cerebrovascular accidents, pain, migraine or various cephalalgias (R. Glennon, Neurosci. Biobehavioral Reviews, **14**, 35, 1990).

Numerous recent pharmacological studies have demonstrated the diversity of the serotonin receptors as well as their respective involvement in various modes of action (cf. E. Zifa, G. Fillion, Pharm. Reviews, **44**, 401, 1992; S. Langer, N. Brunello, G. Racagni, J. Mendlewicz,

VERIFIED TRANSLATION OF PCT

16074/97

IN THE MATTER OF an Australian Application corresponding to PCT Application PCT/FR97/00203

I, Abraham SMITH DipIng DipDoc,
c/o Europa House, Marsham Way, Gerrards Cross, Buckinghamshire, England, do solemnly and sincerely declare that I am conversant with the English and French languages and am a competent translator thereof, and that to the best of my knowledge and belief the following is a true and correct translation of the PCT Application filed under No. PCT/FR97/00203.

Date: 10 July 1998

A. SMITH
For and on behalf of RWS Translations Ltd.

"Serotonin receptor subtypes: pharmacological significance and clinical implications", Karger Ed. (1992); B.E. Leonard, Int. Clin. Psycho-pharmacology, 7, 13-21 (1992); R.W. Fuller, J. Clin. Psychiatry, 53, 36-45 (1992); D.G. Grahame-Smith, Int. Clin. Psychopharmacology, 6, suppl. 4, 6-13, (1992). These receptors are subdivided mainly into 4 large classes ($5HT_1$, $5HT_2$, $5HT_3$ and $5HT_4$) which themselves comprise subclasses like the $5HT_1$ receptors which are subdivided mainly into $5HT_{1A}$, $5HT_{1B}$, $5HT_{1D}$ (cf. G.R. Martin, P.A. Humphrey, Neuropharmacol., 33, 261, 1994; P.R. Saxena, Exp. Opin. Invest. Drugs, 3(5), 513, 1994). The $5HT_{1D}$ receptors themselves contain several receptor subtypes; accordingly, the $5HT_{1Da}$ and $5HT_{1Db}$ receptors have been cloned and then identified in humans (cf. for example E. Hamel et al., Mol. Pharmacol., 44, 242, 1993; G.W. Rebeck et al., Proc. Natl. Acad. Sci. USA, 91, 3666, 1994). Moreover, it has recently been demonstrated that the $5HT_{1B}$ receptors in rodents and $5HT_{1D}$ receptors in other species were capable of controlling the release of serotonin in nerve endings (cf. M. Briley, C. Moret, Cl. Neuropharm. 16, 387, 1993; B.E. Leonard, Int. Clin. Psychopharmacol., 9,7, 1994) as well as the release of other neurotransmitters such as norepinephrine, dopamine or acetylcholine (M. Harrington, J. Clin. Psychiatry, 53, 10, 1992).

Compounds having a selective antagonistic activity at the level of the central $5HT_{1D}$ receptors, such as the novel compounds described in the present invention, can therefore exert a beneficial effect on subjects suffering from disorders of the central nervous system. In particular, such compounds find their usefulness in the treatment of locomotion disorders, depression, anxiety, panic attacks, agoraphobia, obsessive compulsive disorders, memory disorders including dementia, amnesia, and appetite disorders, sexual dysfunctions, pain, Alzheimer's disease, and Parkinson's disease. The $5HT_{1D}$ antagonists also find their usefulness in the treatment of endocrinal

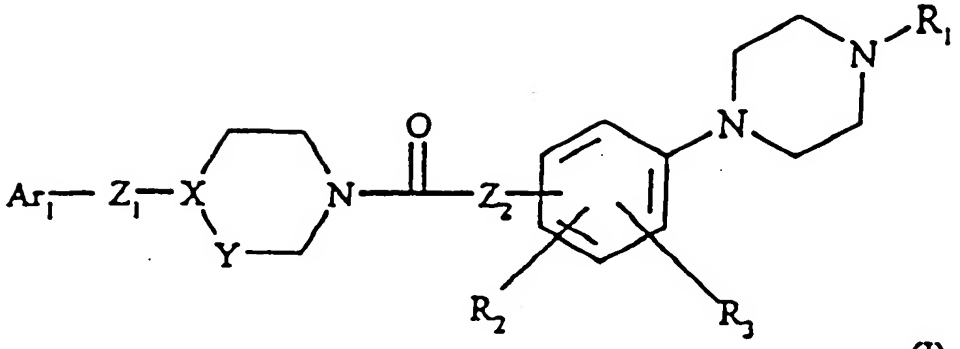
disorders such as hyperprolactinemia, the treatment of vasospasms, of hypertension and of gastrointestinal disorders in which changes in motility and secretion are involved.

The compounds according to the present invention are potent and selective antagonists of the $5HT_{1D}$ receptors and more particularly of the receptors recently identified as $5HT_{1Dα}$ and $5HT_{1Dβ}$ in humans and, as a result, find their usefulness, alone or in combination with other molecules, as drugs and, more particularly, as therapeutic means for the treatment, both curative and preventive, of disorders linked to serotonin.

The prior state of the art in this field is illustrated in particular by patents EP-0,533,266, EP-0,533,267 and EP-0,533,268, GB-2,273,930, WO-9415920, GB-2,276,160, GB-2,276,161, GB-2,276,162, GB-2,276,163, GB-2,276,164, GB-2,276,165, WO-9504729, WO-9506044, WO-9506637, WO-9511243 and F 9408981 which describe aromatic derivatives as $5HT_{1D}$ antagonists and the recent publications which describe GR 127,935 as a $5HT_{1D}$ antagonist (cf. M. Skingle et al., J. of Psychopharm. 8(1), 14, 1994; S. Starkey, M. Skingle, Neuropharmacol., 33, 393, 1994).

The derivatives of the present invention are distinguished from the prior art not only by their novel chemical structure which distinguishes them without ambiguity from the derivatives previously described, but also by their novel biological profile, in particular as regards their selectivity and their effectiveness as antagonists at the level of the serotonin receptor subtypes ($5HT_{1Dα}$ and $_β$).

The present invention relates to the products of general formula (I)



(I)

in which:

R_1 represents a hydrogen or a linear or branched alkyl comprising from 1 to 6 carbon atoms,

Z_2 represents O, NH, CH_2O or CH_2NH,

R_2 and R_3, which are identical or different, represent a hydrogen or a group chosen from a linear or branched alkyl, an alkoxy, thioether, nitrile, trifluoromethyl or halogen (F, Cl, Br, I), or, R_2 and R_3, when they are adjacent, taken together, form a 5- or 6-membered ring so as to constitute, for example, a naphthyl, a tetrahydronaphthyl, a benzopyran or a benzodioxane,

X-Y represents NCH_2, $CH-CH_2$, C=CH, N or NCH_2CH_2,

Z_1 represents $-(CH_2)_n-$, $-(CH_2)_n CO-$, $-CO-$, $-CO(CH_2)_n-$, $-SO_2-$, $-SO_2(CH_2)_n-$, $-O(CH_2)_n-$, $-O(CH_2)_nCO-$, $-OCO-$, $-NH(CH_2)_n-$, $-NH(CH_2)_nCO-$, $-NHCO-$, $-NHCO(CH_2)_n-$, $-NH(CH_2)_nSO_2-$, $-NHSO_2-$, $-NHSO_2(CH_2)_n-$, $-CH=CHCO-$, $-CCCO-$ $-(CH_2)_nSO_2-$, $-O(CH_2)_nSO_2-$.

In the specific case where X-Y represents $CH-CH_2$, Z_1 may also represent -O-,

$-NH-$, $-CONH-$, $-SO_2NH-$, $-OCONH-$, $-NHCOO-$, $NHCONH-$ $-(CH_2)_nNH-$, $-(CH_2)_nO-$, $-CO(CH_2)_nNH-$, $-NH(CH_2)_nO-$, $-NH(CH_2)_nNH-$, $-O(CH_2)_nNH-$, $-O(CH_2)_nO-$, $-CO(CH_2)_nO-$, $-SO_2(CH_2)_nNH-$, $-SO_2(CH_2)_nO-$, $-(CH_2)_nSO_2NH-$, $-(CH_2)_nCONH-$, $-O(CH_2)_nSO_2NH-$, $-O(CH_2)_nCONH-$, $-NH(CH_2)_nSO_2NH-$, $-NH(CH_2)_nCONH-$, $-NHCO(CH_2)_nNH-$, $-NHSO_2(CH_2)_nNH-$ in which n represents an integer between 1 and 6,

In the specific case where X-Y represents $CH-CH_2$ or C=CH, Z_1 may also represent $-CH=CH-$, $-CC-$,

Ar_1 represents an aromatic residue (phenyl, naphthyl or pyridyl) which may be variously substituted, for example, with one or more groups chosen from a linear or branched alkyl comprising from 1 to 6 carbon atoms, a trifluoromethyl, a trifluoromethoxy, a 2,2,2-trifluoroethyl, a phenyl, a benzyl, a cycloalkyl comprising from 3 to 7 carbon atoms, a hydroxyl, a thiol, an alkoxy (OR_4), thioether (SR_4), a nitro (NO_2), a nitrile (CN), an amine (NH_2 or NR_4R_4'), an amine derivative ($NHCOR_4$, $NHSO_2R_4$, $NHCONR_4R_4'$, $NHCO_2R_4$, $NHSO_2NR_4R'_4$), a halogen (fluorine, chlorine, bromine or iodine), a carbonyl (COH, COR_4, $COOR_4$, $CONR_4R'_4$) or a heterocycle which may be optionally substituted such as a 5-membered heterocycle which may contain from 1 to 4 heteroatoms chosen from oxygen, sulfur or nitrogen or with two substituents on adjacent carbons which may form a ring with the aromatic residue to which they are attached, or alternatively the residue Ar-Z_1 represents a tetrahydronaphthyl whose bonding with X uses a saturated carbon,

R_4 represents a linear or branched alkyl residue comprising from 1 to 6 carbon atoms, R'_4 represents a hydrogen or a linear or branched alkyl residue comprising from 1 to 6 carbon atoms

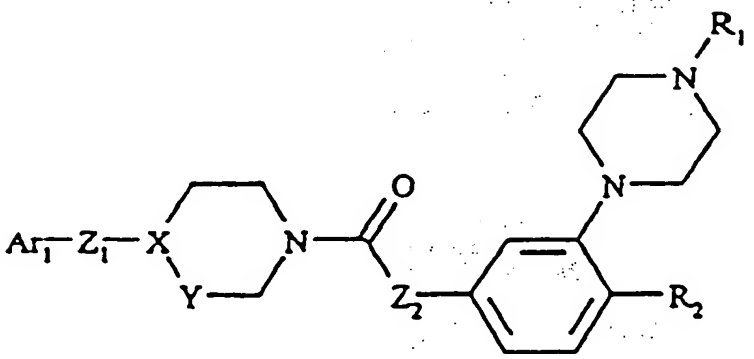
and their salts hydrates, solvates and bioprecursors which are physiologically acceptable for therapeutic use.

The geometric and optical isomers of the compounds of general formula (I) are also included in the present invention as well as a mixture thereof in racemic form.

Among the physiologically acceptable salts of the compounds of general formula (I) are included the salts obtained by addition of organic or inorganic acids such as hydrochlorides, hydrobromides, sulfates, phosphates, benzoates, acetates, naphthoates, p-toluenesulfonates, methanesulfonates, sulphamates, ascorbates, tartrates, citrates, oxalates, maleates, salicylates, fumarates, succinates, lactates, glutarates and glutaconates.

The expression "bioprecursors" as used in the present invention applies to compounds whose structure differs from that of the compounds of formula (I) but which, administered to an animal or to a human being, are converted in the body to a compound of formula (I).

A particularly valued class of compounds of formula (I) corresponds to the compounds of formula (Ia)



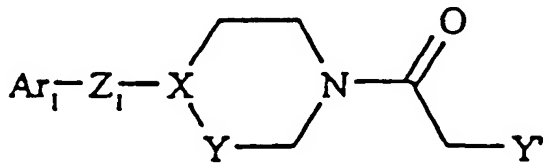
(Ia)

in which Ar_1, Z_1, X-Y, Z_2 and R_1 are as defined in formula I and R_2 represents a CH_3 or OCH_3 radical or a chlorine.

The compounds of the present invention may be prepared by various methods which will be dependent on the nature of Ar_1, Z_1, X, Y, Z_2 and R_1.

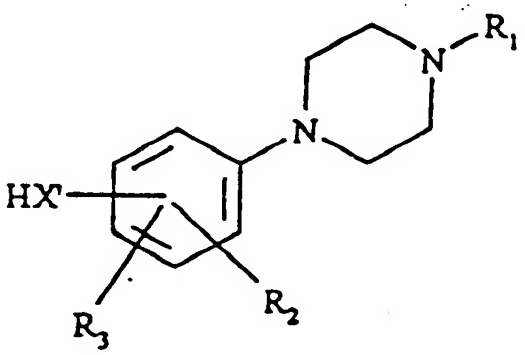
It will be understood that in some chemical reactions or successions of chemical reactions which lead to the preparation of compounds of general formula (I) it is necessary or desirable to protect sensitive groups which may exist in the synthesis intermediates so as to avoid undesirable side reactions. This may be carried out by the use (introduction and deprotection) of conventional protecting groups (such as those described in "Protective groups in Organic Synthesis", T.W. Greene, John Wiley & Sons, 1981 and "Protecting Groups", P.J. Kocienski, Thieme Verlag, 1994. The appropriate protecting groups will therefore be introduced and removed in the step which is most appropriate for this and using the methods and techniques described in the references cited above.

The compounds of general formula (I) in which Ar_1, Z_1, X-Y, R_1, R_2 and R_3 are described as above, and Z_2 represents $-CH_2O-$ or $-CH_2NH-$ are prepared by condensation of an intermediate of formula (II):



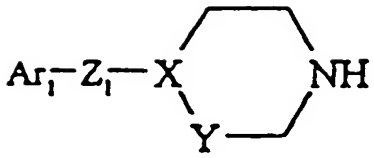
(II)

in which Ar_1, Z_1 and X-Y are as defined above and Y' represents a leaving group such as a halogen (chlorine, bromine or iodine), a tosylate, a mesylate or a triflate with an arylpiperazine of general formula (III):



(III)

in which X' represents O or NH and R_1, R_2 and R_3 are as defined above. The condensation of the arylpiperazines of formula (III) with the electrophiles of formula (II) is carried out in the presence of an organic or inorganic base such as NaH, KH, DiPEA, DBU, pyridine, DMAP, K_2CO_3, $CaCO_3$, Cs_2CO_3, optionally in the presence of an iodide such as NaI, KI, Bu_4NI, in a polar anhydrous solvent such as THF, DME, n-butanol, t-butanol, DMF, DMSO, methyl ethyl ketone, at a temperature of between 20° and 80°. The intermediates of general formula (II) are easily prepared by condensation of a cyclic amine of general formula (IV)



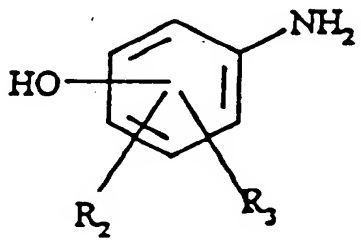
(IV)

in which Ar_1, Z_1, X-Y are as defined above with an acid chloride of general formula (V):

(V)

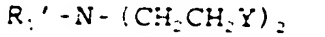
in which Y' is as described above, in the presence of an organic or inorganic base such as pyridine, DiPEA, DMAP, DBU, K_2CO_3, Cs_2CO_3 or $CaCO_3$ in a polar aprotic anhydrous solvent such as THF, DMF, DME, DMSO or methyl ethyl ketone at a temperature of between -10°C and 30°C.

The intermediates of general formula (III) are prepared by various methods and techniques well known to persons skilled in the art for the preparation of arylpiperazines and the choice of which is dependent on the nature of X' and of R_1, R_2 and R_3. Accordingly, in the specific case where X' is an oxygen, the intermediates of formula (III) are accessible by condensation of an arylamine of formula (VI):



(VI)

in which R_2 and R_3 are as defined above, with an amine derivative of formula (VII):

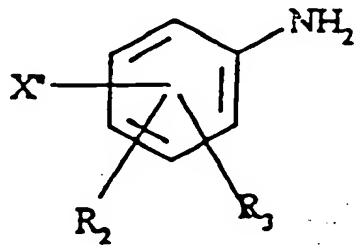


(VII)

in which R'_1 is equivalent to R_1 as defined above or R'_1 represents a protecting group such as a t-butoxycarbonyl or a tosyl (which will be subsequently converted to R_1)

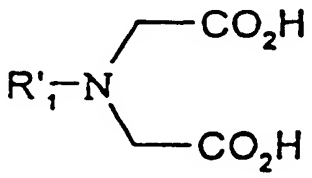
and Y represents a chlorine, a bromine, an iodine, a tosylate or a mesylate. This reaction is preferably carried out in a polar anhydrous solvent such as DMF, acetonitrile, THF, n-butanol, t-butanol or DMSO, generally at the reflux temperature of the solvent used, in the presence of an organic or inorganic base generally used for this type of reaction, such as a potassium, sodium or calcium carbonate.

The compounds of general formula (III) in which X' represents NH are prepared by condensation of an aromatic amine of general formula (X)



(X)

in which R_2 and R_3 are as defined above and X'' represents a functional group which may be subsequently converted to an amine (such as for example a nitro group) either with a bis(haloethyl)amine derivative of formula (VII) under the conditions described above for this type of reaction, or with an amino acid of general formula (XI)

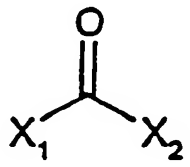


(XI)

in which R'_1 is as defined above, in the presence of acetic anhydride, followed by the reduction of the intermediate diketopiperazine thus formed with, for example, a borane. In both cases, the derivative of formula (III) will be finally obtained after converting the group represented by X'' to an amine. If it is a nitro group, this conversion will be carried out according to methods and techniques well known to persons

skilled in the art for converting a nitroaromatic to an aniline derivative such as, for example, the use of Raney Nickel or of rhodium catalyst in the presence of hydrazine, hydrogenation on palladium-carbon at atmospheric pressure, or the use of $SnCl_2$ or zinc.

The compounds of general formula (I) in which Ar_1, Z_1, X-Y, R_1, R_2 and R_3 are as described above and Z_2 represents O or NH are prepared by condensation of an intermediate of general formula (III) in which X' represents O or NH, and R_1, R_2 and R_3 are as defined above, and of a cyclic amine of formula (IV) in which Ar_1, Z_1 and X-Y are as defined above, with a derivative of general formula (XII):



(XII)

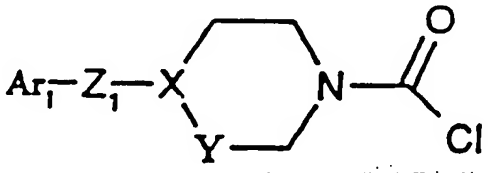
in which X_1 and X_2, which are identical or different, each represent a leaving group such as a halogen (in particular chlorine), an O-alkyl group (in particular the $OCCl_3$ group), a succinimyl, phthalyl or imidazolyl group. The method of the present invention also comprises the use of well-known precursors or analogs of the reagents of general formula (XII). Accordingly and by way of example, the condensation of the intermediates (III) and (IV) with phosgene may be advantageously carried out with the aid of diphosgene or of triphosgene according to a procedure well known to persons skilled in the art.

The methods and techniques chosen for carrying out the preparation of the compounds of formula (I) in which Z_2 represents O or NH by condensation of the derivatives of formulae (III) in which X' represents O or NH and the derivatives of formula (IV) with a reagent of formula (XII) such as the choice of the order of the reagents, the reaction times, the isolation and/or purification of

the intermediates, the reaction temperature at different condensation stages, the nature of the solvent(s), the presence of co-reagents (such as an organic or inorganic base, for example a tertiary amine) or of catalysts and the choice of the reagent (XII) (choice of X_1 and X_2) will be determined by the nature of Ar_1, Z_1, Z_2 (O or NH), X-Y and R_1.

Accordingly, a particularly valued method for the preparation of the derivatives of formula (I) in which Z_2 = NH and Ar_1, Z_1, X-Y and R_1, R_2 and R_3 are as defined above, consists in reacting an intermediate of formula (III) in which X' represents NH with triphosgene in the presence of a base such as triethylamine in an anhydrous solvent such as dichloromethane and then adding a compound of formula (IV) in which Ar_1, Z_1 and X-Y are as defined above in the presence of a base such as a tertiary amine.

In the case of the preparation of derivatives of general formula (I) in which Ar_1, Z_1, X-Y and R_1, R_2 and R_3 are as defined above and Z_2 represents an oxygen, a particularly valued method consists in first condensing a cyclic amine of formula (IV) with triphosgene in the presence of triethylamine in an anhydrous solvent such as dichloromethane and isolating the intermediate of general formula (XIII) thus formed:

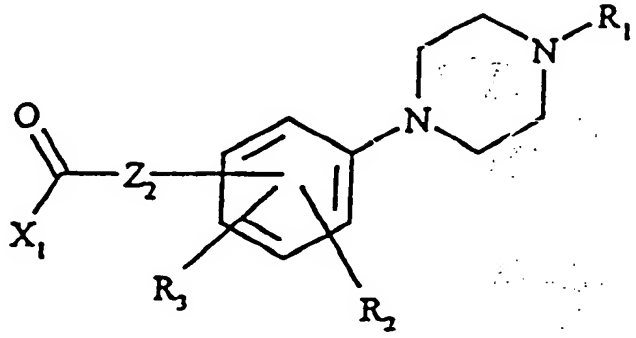


(XIII)

before condensing it with a nucleophile of general formula (III) in which X' represents an oxygen, in the presence of an organic or inorganic base such as NaH, KH, t-BuOK in a polar aprotic solvent such as THF or DMF.

The methods which make it possible to prepare the products of formula (I) in which Z_2 represents O or NH by condensation of a cyclic amine of formula (IV) with a

derivative of general formula (XIV):

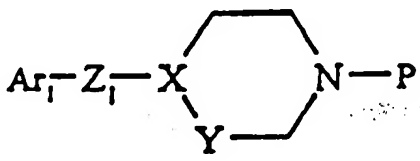


(XIV)

in which X_1, R_1, R_2 and R_3 are as defined above and Z_2 represents O or NH, in the presence of an organic or inorganic base in an aprotic polar solvent at a temperature of between 20°C and 100°C, should also be considered as being included in the present invention.

The intermediates of general formula IV in which Ar_1, Z_1 and X-Y are as defined above are prepared in general by various methods and techniques well known to persons skilled in the art, as described for example in Patents DE 2,801,195, EP 7067 (800123), EP 12643 (800625), FR 2,459,795 (810116), EP 372776 (900613), FR 2,678270 (921231), FR 2,675,801 (921030), EP 580398 (940126), WO 9401403 (940120) as well as the publications J. Med. Chem 34, 3011, (1991); J. Chem. Soc. Chem. Comm. 2, 142, (1989); Tetrahedron 47, 5161 (1991); Synthesis 11, 1023 (1991); Izobretaniya 37, 89 (1992) and Tetrahedron Lett. 35, 973, (1994).

A particularly valued method for the preparation of the cyclic amines of formula (IV), in the context of the present invention, consists in preparing these derivatives from precursors of general formula XV.

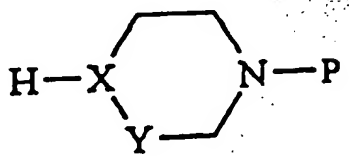


(XV)

in which Ar_1, Z_1 and X-Y are as defined above and P

represents a protecting group normally used for protecting a secondary amine such as, for example, a benzyl, a benzyl in which the aromatic is substituted, an acetyl, a trifluoroacetyl, a benzyloxycarbonyl or a t-butoxycarbonyl. The methods used for converting the precursor of general formula (XV) to a cyclic amine IV will obviously depend on the nature of P, and are described in "Protective Groups in Organic Synthesis" T.W. Greene, John Wiley & Sons, 1981 or "Protecting Group" P.J. Kocienski, Thieme Verlag, 1994. It is clearly understood that the choice of the nature of the protecting group P will be determined according to the methods and techniques used for the preparation of the intermediates of formula XV.

In the specific case where X-Y represents NCH_2, N or NCH_2CH_2, a particularly valued method for the preparation of the compounds of formula XV consists in condensing an intermediate of formula XVI



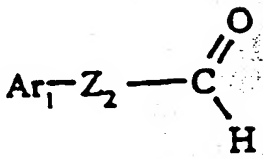
(XVI)

in which P represents a group for protecting an amine as described above, with an electrophile of formula XVII

$$Ar_1 - Z_1 - L \qquad \text{(XVII)}$$

in which Ar_1 and Z_1 are as defined above and L represents a leaving group. The nature of L and the experimental conditions used to carry out this condensation will depend in particular on the nature of Z_1. Accordingly, in the case where Z_1 represents $-(CH_2)_n-$, $O(CH_2)_n-$, $CO(CH_2)_n$, $NH(CH_2)_n$, $NHCO(CH_2)_n$, $SO_2(CH_2)_n$, $NHSO_2(CH_2)_n$; this condensation may be carried out between an intermediate of formula (XVI) and an electrophile of formula (XVII) in which L will be chosen from Cl, Br, I, OTs, OMs and OTf, in the presence of an organic base (such as for example

a tertiary amine) or an inorganic base (such as for example Cs_2CO_3, K_2CO_3 or Na_2CO_3) in a polar anhydrous solvent such as THF, DME, DMF or DMSO, isopropanol or t-butanol, at a temperature of between 0°C and 80°C. An alternative but particularly valued method for the preparation of these same derivatives of formula (XV) in which X represents a nitrogen and Z_1 represents $(CH_2)_n$, $NH(CH_2)_n$, $O(CH_2)_n$, $SO_2(CH_2)_n$, $NHSO_2(CH_2)_n$ or $NHCO(CH_2)_n$ consists in condensing a cyclic amine of formula (XVI) in which X represents a nitrogen with an aldehyde of formula XVIII:



(XVIII)

in which Ar_1 is as defined above and Z_2 represents a residue Z_1 truncated from a methylene, under the conditions well known by the name "reductive amination" such as, for example, those described in Synlett, 1079, 1995. In the case where Z_1 represents $(CH_2)_nCO$, $O(CH_2)_nCO$, $NH(CH_2)_nCO$, CH = CHCO, CCCO, CO or $SO_2(CH_2)_nCO$, condensation of a cyclic amine of formula XVI will be carried out with a carboxylic acid derivative of formula (XVII) in which L represents a chlorine or alternatively the intermediate (XVII) represents an activated form of a carboxylic acid suitable for the formation of an amide by reacting with an amine by the methods and techniques well known to persons skilled in the art for this type of conversion. In the case where Z_1 represents $NHSO_2$, SO_2, $O(CH_2)_nSO_2$ $NH(CH_2)_nSO_2$ or $(CH_2)_nSO_2$, the intermediates of formula (XVI) are condensed with sulfonyl chlorides of formula XVII in which L represents Cl, by the methods well known to persons skilled in the art for preparing a sulfonamide from a sulfonyl chloride and an amine.

In the case of the compounds of formulae (XV) in which Ar_1, and P are as defined above, X represents a nitrogen and Z_1 represents OCO or NHCO, the methods of preparation

consist, for example, in condensing either a phenol (Ar_1OH), or an aniline (Ar_1NH_2) and an amine of formula (XVI) with a reagent of formula XII by the methods and techniques previously described for the preparation of carbamates and ureas.

In the specific case where Ar_1Z_1 represents a tetrahydronaphthyl in which the bonding with X uses a saturated carbon and X represents a nitrogen, a valued method of preparation of an intermediate of formula (XV) consists in condensing the appropriate tetralone with a cyclic amine of formula XVI, in the presence of p-toluenesulfonic acid in a solvent such as toluene under reflux, followed by the reduction of the enamine thus formed, for example, by catalytic hydrogenation under a hydrogen pressure in the presence of palladium or platinum oxide on carbon.

A particularly valued method of preparing the intermediates of formula (XV) in which X-Y represents NCH_2, N or NCH_2CH_2 and Z_1 represents $(CH_2)_n$, $O(CH_2)_n$, $NH(CH_2)_n$, $SO_2(CH_2)_n$ consists in reducing the amides of formula (XV) in which Z_1 represents respectively $(CH_2)_{n-1}CO$, $O(CH_2)_{n-1}CO$, $NH(CH_2)_{n-1}CO$, $SO_2(CH_2)_{n-1}CO$ by methods known to allow the reduction of an amide to an amine, such as the use of an aluminum hydride (for example $LiAlH_4$) in a solvent such as THF or ethyl ether.

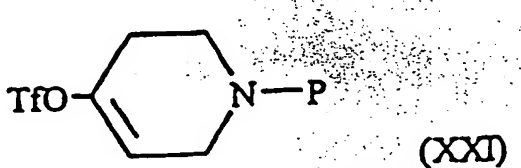
The intermediates of general formula (XV) in which Ar_1 and P are as defined above and X-Y represents C=CH and Z_1 represents $(CH_2)_n$, $O(CH_2)_n$ or CH=CH are prepared by coupling an organometallic of formulae XIX or XX

$$Ar_1 - Z_1 - M \qquad \text{(XIX)}$$

$$Ar_1 - Z_1 - M' - Z_1 - Ar \qquad \text{(XX)}$$

in which M represents ZnBr, SnR_3 where R represents an alkyl group such as a butyl or $B(OR')_2$ where R' repre-

sents a hydrogen or an alkyl and M' represents Zn, with a vinyl triflate of formula (XXI)



(XXI)

in the presence of a palladium derivative such as for example $Pd(PPh_3)_4$, optionally of a base such as a tertiary amine, a potassium, sodium or cesium carbonate, of lithium chloride when M = SnR_3 and in a polar aprotic solvent such as THF, DME or DMF at a temperature of between 20° and 80°C (cf. "Organometallics in synthesis", M. Schlosser, John Wiley & Son, 1994). The intermediate triflates of formula XXI are prepared, for example, by the method described in Synthesis 993, 1991.

The intermediates of formula XV in which Z_1 represents an ethynyl residue and X represents C=CH are prepared by coupling triflates of formula XXI with an aromatic acetylene of formula XXII

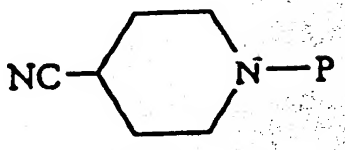
$$Ar - C \equiv C - H \qquad \text{(XXII)}$$

in the presence of a palladium catalyst such as $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$, of a base such as a secondary or tertiary amine, a potassium, sodium or cesium carbonate and optionally of copper iodide in a polar solvent such as DMSO, DMF, THF (cf. Organic Preparation and Procedures int., 27(2), 127-160, 1995).

The intermediates of general formula (XV) in which Ar_1 and P are as defined above, X-Y represents $CH-CH_2$ and Z_1 represents $(CH_2)_n$, $O(CH_2)_n$ may be prepared from the intermediates of general formula (XV) in which Ar_1 and P are as defined above, X-Y represents C=CH and Z_1 represents $(CH_2)_n$, $O(CH_2)_n$, CC or CH=CH by reducing the double and triple bonds by catalytic hydrogenation (for example H_2, Pd/C).

The derivatives of formulae XV in which Z_1 represents CO, $(CH_2)_nCO$ or $O(CH_2)_nCO$ and X-Y represents C=CH are prepared by coupling an intermediate of formula XIX in which Z_1 is omitted or represents $(CH_2)_n$, $O(CH_2)_n$ and M represents SnR_3 where R represents an alkyl group with a triflate of formula XXI, in the presence of a palladium catalyst such as $Pd(PPh_3)_4$ optionally of lithium chloride and of a base such as potassium carbonate under carbon monoxide pressure in the polar solvent such as THF according to the method described in "Organometallics in synthesis", M. Schlosser, John Wiley & Son, 1994.

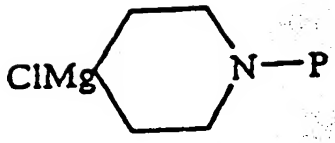
The intermediates of formula XV in which Z_1 represents CO and X-Y represents $CH-CH_2$ are prepared by condensation of an aromatic derivative "Ar_1H" with an acid chloride, according to the methods and techniques known by the name of Friedel-Crafts reaction, as described for example in J. Med. Chem. 33, 903, 1990. An alternative method (the choice of which will depend essentially on the nature of Ar_1) of preparing compounds of formula XV in which Z_1 represents CO and X-Y represents $CH-CH_2$ consists in condensing an organometallic derivative Ar_1-M in which M represents MgCl, MgBr or Li with a nitrile of formula XXIII



(XXIII)

in a polar anhydrous solvent such as ethyl ether, THF or DME, at a temperature of between -20°C and 60°C, followed by acid hydrolysis of the reaction medium.

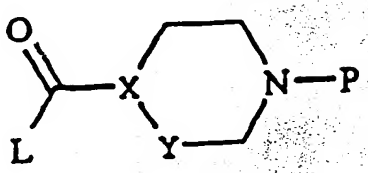
The intermediates of general formula (XV) in which Z_1 represents $(CH_2)_n$, $O(CH_2)_n$, $NH(CH_2)_n$, $SO_2(CH_2)_n$ and X-Y represents $CH-CH_2$ may also be prepared by condensation of a nucleophile of general formula XXIV



(XXIV)

(a method of preparation of which is described in Patent US 4,335,127; 1982) with a derivative of formula XVII in which Z_1 represents $(CH_2)_n$, $O(CH_2)_n$, $SO_2(CH_2)_n$ and L is as defined above.

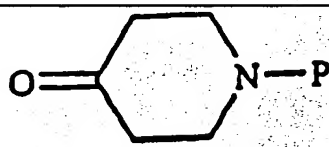
In the specific case where Z_1 represents OCO or NHCO and X-Y represents CH-CH_2 or C=CH, a valued method of preparation of the intermediates of formula (I) consists in condensing a phenol (Ar_1OH) or an aniline (Ar_1NH_2) with a derivative of formula XXV



(XXV)

in which L and the carboxyl to which it is attached constitute the activated form of a carboxylic acid suitable for the formation of an amide or of an ester by condensation with an amine or an alcohol by methods and techniques well known to persons skilled in the art.

In the specific case where Z_1 represents NH and X-Y represents CH-CH_2, the intermediates of formula XV are prepared by a reductive amination reaction, using for example $NaBH_4$ or $NaBH_3CN$ as reducing agent, between an aniline of formula Ar_1NH_2 and a piperidone of formula XXVI

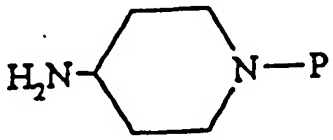


(XXVI)

in which P is as defined above.

In the specific case where X-Y represents CH-CH_2 and Z_1

represents CONH, SO_2NH, $(CH_2)_nNH$, $CO(CH_2)_nNH$ or $O(CH_2)NH$, the intermediates of formula XV are prepared by condensation of an aminopiperidine of formula XXVII



(XXVII)

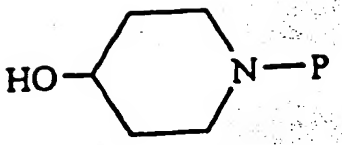
with an electrophile of formula XXVIII

$$Ar_1Z'_1\text{-}L \qquad \text{(XXVIII)}$$

in which Z'_1 represents Z_1 truncated from the terminal NH residue and L is as defined above. This condensation will be carried out by different techniques and methods which will depend on the nature of Z'_1 and L and which are similar to the techniques and methods previously described for the condensation of the intermediates XVI and XVII (in which X represents a nitrogen). The reductive amination reaction as described above may also be carried out for the preparation of compounds of formula XV in which Z_1 represents $(CH_2)_nNH$, $O(CH_2)_nNH$ or $SO_2(CH_2)_nNH$ from the amines of formula XXVII and aldehyde respectively of formulae $Ar_1(CH_2)_{n-1}CHO$, $Ar_1O(CH_2)_{n-1}CHO$ or $SO_2(CH_2)_{n-1}CHO$ or from amines of formula $Ar_1(CH_2)_nNH_2$, $Ar_1O(CH_2)_nNH_2$ or $Ar_1SO_2(CH_2)_nNH_2$ with the piperidone XXVI.

The intermediates of formula XV in which Z_1 represents OCONH or NHCONH and X-Y represents $CH\text{-}CH_2$ are prepared by condensation of an aminopiperidine of formula XXVII and of a phenol (Ar_1OH) or of an aniline (Ar_1NH_2) with an electrophile of formula XII according to the methods and techniques previously described for the preparation of carbamates or ureas.

In the specific case where Z_1 represents O and X-Y represents $CH\text{-}CH_2$, the intermediates of formula XV are prepared by a Mitsunobu reaction from a derivative Ar_1OH and a hydroxylated derivative of piperidine of formula (XXIX)



(XXIX)

in which P is as defined above.

In the specific case where X-Y represents CH-CH_2 and Z_1 represents $(CH_2)_nO$, $O(CH_2)_nO$, $NH(CH_2)_nO$, $CO(CH_2)_nO$ or $SO_2(CH_2)_nO$, the intermediates of formula XV are prepared by condensation of a hydroxypiperidine of formula (XXIX) with an electrophile of formula (XXVIII) in which Z'_1 represents Z_1 truncated from a terminal oxygen and L represents a leaving group such as a halogen (chlorine, bromine or iodine), a tosylate, a mesylate or a triflate. This condensate may be carried out in the presence of an organic base (such as a tertiary amine, potassium t-butoxide or butyllithium) or an inorganic base (for example NaH, KH, Cs_2CO_3) in a polar anhydrous solvent such as THF, DME, DMF, DMSO, t-butanol, at a temperature of between -15°C and 80°C.

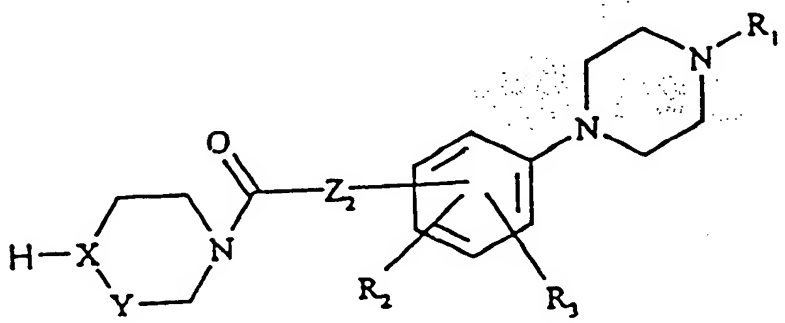
The intermediates of formula XV in which Z_1 represents NHCOO and X-Y represents CH-CH_2 are prepared by condensation of an alcohol of formula (XXIX) and of an aniline derivative (Ar_1NH_2) with a reagent of formula XII according to the methods and techniques previously described for the preparation of a carbamate.

The intermediates of formula XV in which Z_1 represents $NHSO_2$, SO_2, $(CH_2)_nSO_2$, $O(CH_2)_nSO_2$ or $NH(CH_2)_nSO_2$ and X-Y represents CH-CH_2 are prepared by condensation of a sulfonyl chloride corresponding to the formula XXX

$$Ar\ Z_1 - Cl \qquad \text{(XXX)}$$

with a nucleophile of formula XXIV in a polar aprotic solvent such as ethyl ether or THF at a temperature of between 0° and 60°C.

Alternative methods of synthesis of the compounds of formula (I) in which X-Y represents NCH_2, N, NCH_2CH_2 which consist in condensing intermediates of general formula (XXXI)



(XXXI)

in which Z_2, R_1, R_2 and R_3 are as defined above with an electrophile of formula (XVII) in which Z_1 and L are as defined above and this according to the methods and techniques described above for the condensation of XVI with XVII and the choice of which will depend essentially on the nature of Z_1, should also be considered as being included in the present invention.

In the specific case of the compounds of formula (I) with X = N and Z_1 = OCO or NHCO, an alternative method of preparation consists in reacting a phenol of formula Ar_1OH or an amine of formula Ar_1NH_2 and an amine of formula (XXXI) as defined above with a compound of formula (XII) by the methods and techniques previously described for the preparation of carbamates and ureas.

In the specific case of the compounds of general formula (I) in which R_1 represents a hydrogen, it is preferable to use, for certain reactions requiring it, reaction intermediates in which R_1 represents a protecting group such as, for example, a t-butoxycarbonyl (BOC) which will be introduced beforehand by condensation of the appropriate intermediate in which R_1 = H with an appropriate reagent such as $(BOC)_2O$, BOC-ON = C(CN)-Ph, $BOC-ONH_2$. This will make it possible to prepare, according to the

methods and techniques presented earlier, intermediates of general formula (I) in which R_1 = BOC and to convert these intermediates to final products of general formula (I) in which R_1=H after deprotection of the t-butoxycarbonyl according to methods and techniques well known for this type of conversion such as the use of acid (HCl, CF_3CO_2H, H_2SO_4) in an organic medium.

All the methods which make it possible to convert a derivative of formula (I) to another derivative of formula (I) in which at least one of the substituents Ar_1, Z_1, X-Y, Z_2, R_1, R_2 or R_3 are different, by methods and techniques well known to persons skilled in the art, should also be considered as forming an integral part of the present invention. Accordingly and by way of example, the derivatives of general formula (I) in which Ar_1 represents a phenyl substituted with an NO_2 group may be converted to derivatives of formula (I) in which Ar_1 represents a phenyl substituted at the same position with an NH_2 group by methods and techniques well known for this type of reduction as described, for example, in "Comprehensive Organic Transformation", p. 412; R.C. Larock, VCH, 1989, among which there may be mentioned atmospheric hydrogenation catalyzed by palladium on carbon, the use of Sn_2Cl_2, of zinc, of Raney Ni or of a rhodium catalyst in the presence of hydrazine. The compounds of general formula (I) in which Ar_1 represents an aromatic substituted with an NH_2 group may themselves be converted to numerous other derivatives of formula (I) such as derivatives in which Ar_1 represents an aromatic substituted with NR_4R_4', $NHCOR_4$, $NHCO_2R_4$, $NHCOR_4$, $NHSO_2R_4$, $NHSO_2OR_4$ or $NHSO_2NR_4R_4'$ by methods and techniques well known for converting an aromatic amine to an amide, carbonate, urea, sulfonamide, sulfonate or sulfonylurea.

When it is desired to isolate a compound according to the invention in the form of a salt, for example of a salt by addition with an acid, this can be achieved by treating the free base of general formula (I) with an appropriate

acid, preferably in an equivalent quantity, or with creatinine sulfate in an appropriate solvent.

When the processes described above for preparing the compounds of the invention give mixtures of stereoisomers, these isomers may be separated by conventional methods such as preparative chromatography.

When the novel compounds of general formula (I) possess one or more asymmetric centers, they may be prepared in the form of a racemic mixture or in the form of enantiomers whether by enantionselective synthesis or by resolution. The compounds of formula (I) possessing at least one asymmetric center may, for example, be separated into their enantiomers by the usual techniques such as the formation of diastereomeric pairs by formation of a salt with an optically active acid such as (+)-di-*p*-toluoyl-l-tartaric acid, (+)-camphorsulfonic acid, (-)-camphorsulfonic acid, (+)-phenypropionic acid, (-)-phenylpropionic acid, followed by fractional crystallization and regeneration of the free base. The compounds of formula (I) in which R_1 is a hydrogen comprising at least one asymmetric center may also be resolved by formation of diastereomeric amides which are separated by chromatography and hydrolyzed to release the chiral auxiliary.

The following examples illustrate the invention without, however, limiting its scope.

The proton NMR spectra were recorded on a Brücker AC 200 apparatus. The chemical shifts are expressed in ppm and the following abbreviations have been used: "s" for singlet: "se" for broad singlet, "d" for doublet, "dd" for doublet of doublet, "t" for triplet, "q" for quadruplet, "sx" for sextuplet, "m" for multiplet, "M" for unresolved complex.

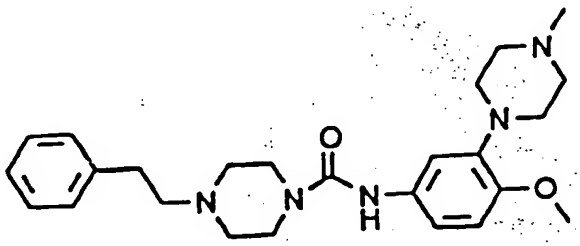
The infrared spectra were recorded on a Nicolet 510P

apparatus. The absorption bands are given in cm^{-1}.

The elemental analyses were carried out on a Fisons EA 1108 apparatus.

EXAMPLE 1

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-phenethylpiperazin-1-ylamide difumarate



1

A solution of 4-methoxy-3-(4-methylpiperazin-1-yl)aniline which may be prepared according to the method described in European Patent 0533266-11 (500 mg, 2.26 mmol) and of triethylamine (315 µl, 2.27 mmol) in dichloromethane (10 ml) is slowly supplied by a cannula-like tube to a solution of triphosgene (225 mg, 0.76 mmol) in dichloromethane (30 ml) under a nitrogen atmosphere. During this operation, the reaction mixture is cooled with an ice bath. It is then brought to room temperature over 20 min before the addition of 4-phenethylpiperazine (430 mg, 2.26 mmol) and triethylamine (315 µl, 2.27 mmol) diluted in dichloromethane (10 ml). After 2 h at room temperature, the mixture is diluted with water and then extracted three times with ethyl acetate. The organic phases are pooled, washed once with a saturated sodium chloride solution, dried over magnesium sulfate and concentrated. The crude product is purified by flash chromatography with a (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 831 mg (Yield: 84%)

This compound is dissolved in methanol and treated with

fumaric acid to give the corresponding fumarate. The latter is crystallized from ether.

Elemental analysis for: $C_{25}H_{35}N_5O_2$-$2C_4H_4O_4$
Calculated values: C 59.18; H 6.47; N 10.46;
Experimental values: C 58.75; H 6.53; N 10.40

Mass: 438 (MH+),248,191,136

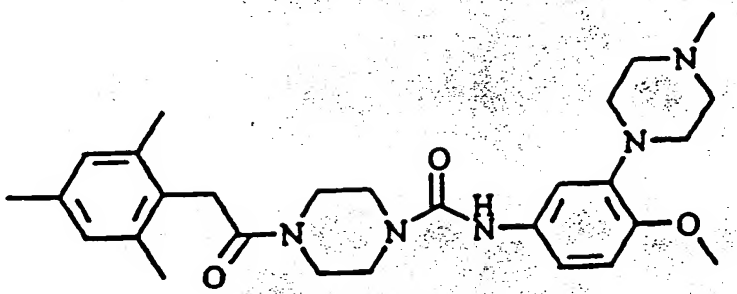
IR (KBr): 3400,3028,1707,1639,1508

1H NMR (DMSO): 2.42-2.48 (m,9h); 2.74 (M,6H); 3.00 (M,4H); 3.35 (M,4H); 3.71 (s,3H); 6.57 (s,4H); 6.79 (d,1H); 7.09-7.31 (m,7H); 8.29 (s,1H).

Melting point: 120°C

EXAMPLE 2

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-(2,4,6-trimethylbenzylcarbonyl)piperazin-1-ylamide fumarate



2

Compound 2a: 1-(2,4,6-trimethylbenzylcarbonyl)-4-(*tert*-butyloxycarbonyl)piperazine

A solution of *tert*-butoxycarbonylpiperazine (1.05 g, 5.61 mmol) and mesitylacetic acid (1.0 g, 5.61 mmol) in dichloromethane (50 ml) is stirred for three days at room temperature in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.08 g, 5.61 mmol), triethylamine (800 ml, 5.61 mmol) and 4-dimethylamino-pyridine (a spatula tip). After diluting in water, the

mixture is extracted three times with ethyl acetate, and then the pooled organic phases are washed with a saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated. The crude product is purified by flash chromatography with a (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 1.7 g (Yield: 88%)

1H NMR ($CDCl_3$): 1.45 (s,9H); 2.18 (s,6H); 2.23 (s,3H); 3.43 (M,4H); 3.56 (M,4H); 3.61 (s,2H); 6.83 (s,2H).

Compound 2b: 1-(2,4,6-trimethylbenzylcarbonyl)piperazine

Trifluoroacetic acid (4.9 ml) is slowly added to a solution of compound 2a (1.7 g; 4.91 mmol) in dichloromethane (25 ml) kept at 0°C. The reaction mixture is then brought to room temperature and the reaction is monitored by thin-layer chromatography. The reaction is complete after 1 h. The trifluoroacetic acid is neutralized with a saturated sodium hydrogen carbonate solution. The phases are separated and the organic phase is washed with a saturated sodium chloride solution, dried over magnesium sulfate and concentrated. The crude reaction product is purified by flash chromatography with a (90/10/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 1.08 g (Yield: 89%)

1H NMR ($CDCl_3$): 1.25 (se,1H); 2.22 (s,6H); 2.25 (s,3H); 2.86 (M,4H); 3.61 (M,6H); 6.85 (s,2H).

Compound 2 : Compound 2 is prepared according to the procedure described in Example 1 from the following reagents: triphosgene (204 mg, 0.69 mmol); 4-methoxy-3-(4-methylpiperazin-1-yl)aniline (555 mg, 2.06 mmol); triethylamine (290 µl×2, 2.06 mmol×2); 1-(2,4,6-trimethylbenzylcarbonyl)piperazine (2b) (506 mg, 2.06 mmol);

dichloromethane (40ml).

The crude product is purified by flash chromatography with a (92/8/1) and then (90/9/1) dichloromethane/ methanol/ammonium hydroxide mixture.

Mass obtained: 756 mg (Yield: 75%)

This compound is dissolved in methanol and treated with fumaric acid to give the corresponding fumarate. The latter is crystallized from ether.

Elemental analysis for: $C_{28}H_{39}N_5O_3-C_4H_4O_4$
Calculated values: C 63.04; H 7.11; N 11.49;
Experimental values: C 62.91; H 7.46; N 11.12

Mass (DCI/NH3) : 494 (MH+), 248,222

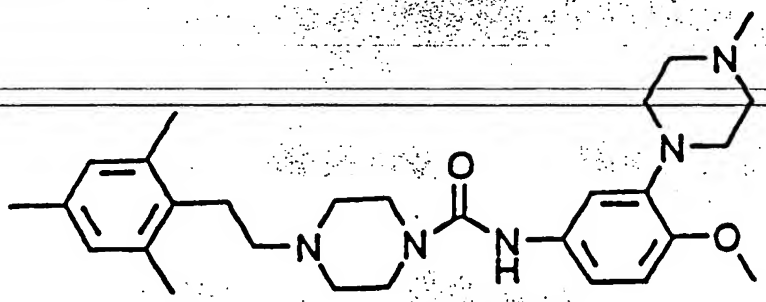
IR (KBr): 3440,3315,3012,2907,2861,1637,1512,1439,1222

1H NMR (DMSO): 2.10 (s,6H); 2.18 (s,3H); 2.32 (s,3H); 2.62 (M,4H); 2.97 (M,4H); 3.47 (M,8H); 3.65 (s,2H); 3.71 (s,3H); 6.55 (s,2H); 6.80 (m,3H); 7.04(m,2H); 8.37 (s,1H).

Melting point: 197°C

EXAMPLE 3

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-(2,4,6-trimethylphenethyl)piperazin-1-ylamide difumarate



3

Compound 3a : 1-(2,4,6-trimethylphenethyl)piperazine

A lithium aluminum hydride solution (3.4 ml) of a 1M solution in ethyl ether, 3.4 mmol) is slowly added to a suspension of compound **2b** (551 mg, 2.24 mmol) in ethyl ether (10 ml). After 1/2 h, the reaction mixture is slowly neutralized with a 3 M solution of sodium hydroxide and then filtered on Celite. The phases are separated and the organic phase is dried over magnesium sulfate, filtered and concentrated. The crude product is purified by flash chromatography with a (90/9/1) dichloromethane/methane/ammonium hydroxide mixture.

Mass obtained : 413 mg (Yield: 79%)

1H NMR ($CDCl_3$): 1.67 (s,1H); 2.25 (s,3H); 2.31 (s,6H); 2.36-2.45 (m,2H); 2.55 (M,4H); 2.78-2.87 (m,2H); 2.96 (t,4.9Hz,4H); 6.84 (s,2H).

Compound 3 : Compound **3** is prepared according to the procedure described in Example **1** from the following reagents: triphosgene (172 mg, 0.58 mmol); 4-methoxy-3-(4-methylpiperazin-1-yl)aniline (384 mg, 1.74 mmol); triethylamine (244 µl×2, 1.74 mmol×2); 1-(2,4,6-trimethylphenethyl)piperazine (**3a**) (403 mg, 1.74 mmol); dichloromethane (40 ml).

The crude product is purified by flash chromatography with a (92/8/1) and then (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained : 792 mg (Yield: 95%)

This compound is dissolved in methanol and treated with fumaric acid to give the corresponding fumarate. The latter is crystallized from ether.

Elemental analysis for: $C_{24}H_{31}N_5O_2 \cdot 2C_4H_4O_4 \cdot 0.64H_2O \cdot 0.5C_4H_{10}O$

Calculated values: C 60.02; H 7.33; N 9.21;
Experimental values: C 59.87; H 7.26; N 9.18

Mass (DCI/NH3) : 480(MH+),248,233,136

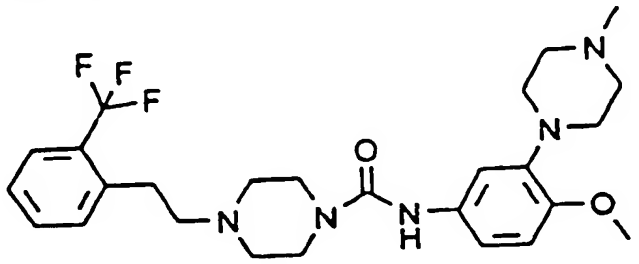
IR (KBr): 3440,2914,1683,1643,1512,1262,985

1H NMR (DMSO): 2.16 (s,3H); 2.23 -s,6H); 2.40 (M,5H); 2.49 (M,4H); 2.74 (M,6H); 3.00 (M,4H); 3.45 (M,4H); 3.72 (s,3H); 6.58 (s,4H); 6.80 (m,3H); 7.05 (m,2H); 8.29 (s,1H)

Melting point: 103°C

EXAMPLE 4

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-(2-trifluoromethylphenethyl)piperazin-1-ylamide fumarate



4

Compound 4a: 1-(2-trifluoromethylbenzylcarbonyl)-4-(tert-butyloxycarbonyl)piperazine

Compound **4a** is prepared according to the same procedure as that described for compound **2a** from the following reagents: (2-trifluoromethylphenyl)acetic acid (1.14 g, 5.56 mmol); 1-tert-butyloxycarbonylpiperazine (1.04 g, 5.56 mmol); 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.07 g, 5.56 mmol); 4-dimethylamino-pyridine (a spatula tip); dichloromethane (50 ml). The crude product is used directly in the next stage.

Mass obtained : 1.92 g (Yield: 93%)

1H NMR (CDCl3) : 1.43 (s,9H); 3.40 (M,6H); 3.62 (M,2H); 3.86 (s,2H); 7.35 (te,7.5Hz,2H); 7.50 (d,7.6Hz,1H); 7.63 (d,7.5Hz,1H).

Compound 4b: 1-(2-trifluoromethylbenzylcarbonyl)-piperazine

Compound **4b** is prepared according to the same procedure as that described for compound **2b** from the following reagents: compound **4a** (1.92 g, 5.15 mmol); trifluoroacetic acid (4.7 ml), dichloromethane (25 ml). The crude product is purified by flash chromatography with a (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained : 866 mg (Yield: 62%)

1H NMR (CDCl3) : 2.75-2.88 (m,4H); 3.41 (t,4.4Hz,2H); 3.64 (t,4.9Hz,2H); 3.87 (s,2H); 7.36 (M,2H); 7.50 (d,7.4Hz,1H); 7.65 (de,8.9Hz,1H).

Compound 4c : 1-(2-trifluoromethylphenethyl)piperazine

Compound **4c** is prepared according to the same procedure as that described for compound **3a** from the following reagents: compound **4b** (866 mg, 3.18 mmol); lithium aluminum hydride (4.8 ml of a 1 M solution in ethyl ether, 4.8 mmol); ethyl ether (15 ml). The crude product is purified by flash chromatography with a (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained : 385 mg (Yield: 45%)

1H NMR (CDCl3) : 1.84 (se,1H); 2.53 (M,6H); 2.92 (M,6H); 7.24-7.62 (m, 4H).

Compound 4 : Compound **4** is prepared according to the procedure described for compound **1** from the following reagents: triphosgene (150 mg, 0.50 mmol); 4-methoxy-3-(4-methylpiperazin-1-yl)aniline (310 mg, 1.10 mmol);

pyridine (130 µl×2, 1.64 mmol×2); 1-(2 trifluoromethyl-phenethyl)piperazine (**4c**) (385 mg, 1.19 mmol); dichloromethane (40 ml).

The crude product is purified by flash chromatography with a (80/20/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained : 423 mg (Yield: 70%)

This compound is dissolved in methanol and treated with fumaric acid to give the corresponding fumarate. The latter is crystallized from ether.

Elemental analysis for: $C_{30}H_{34}F_3N_5O_2 \cdot C_4H_4O_4 \cdot 0.55H_2O$

Calculated values: C 57.05; H 6.24; N 11.09;
Experimental values: C 56.92; H 6.35; N 10.80

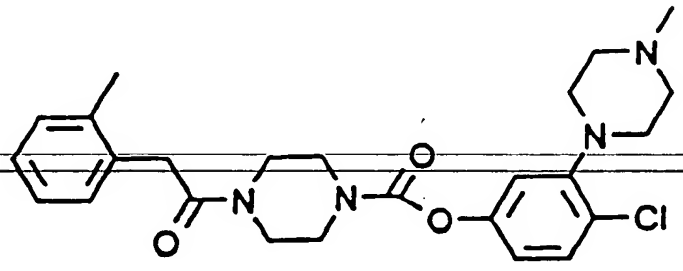
IR (KBr): 3422,2952,2838,1642,1508

1H NMR (DMSO): 2.40 (s,3H); 2.51 (M,6H); 2.72 (M,4H); 3.01 (M,6H); 3.45 (M,4H); 3.74 (s,3H); 6.59 (s,2H); 6.81 (d,8.7Hz,1H); 7.08 (m,2H); 7.40-7.72 (m,4H); 8.31 (s,1H).

Melting point: 124°C

EXAMPLE 5

4-[Chloro-3-(4-methylpiperazin-1-yl]phenyl 4-(2-methyl-benzylcarbonyl)piperazin-1-yloate fumarate



Compound 5a: 1-(2-methylbenzylcarbonyl)-4-(tert-butyloxycarbonyl)piperazine

Compound **5a** is prepared according to the same procedure as that described for compound **2a** from the following reagents: o-tolylacetic acid (500 mg, 3.3 mmol); 1-tert-butyloxycarbonylpiperazine (620 mg, 3.3 mmol); 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (688 mg, 3.3 mmol); triethymamine (460 ml, 3.3 mmol); 4-dimethylaminopyridine (a spatula tip); dichloromethane (30 ml). The crude product is purified by flash chromatography with a (100/0/1) and then (95/5/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained : 803 mg (Yield: 76%)

Elemental analysis for: $C_{19}H_{26}N_2O_4$
Calculated values: C 67.90; H 8.23; N 8.80;
Experimental values: C 67.49; H 8.21; N 8.74

IR (KBr): 2972,2913,1701,1636

1H NMR ($CDCl_3$) : 1.42 (s,9H); 2.25 (s,3H); 3.36 (M,6H); 3.60 (M,2H); 3.73 (s,2H); 7.05-7.15 (m,4H).

Compound 5b: 1-(2-methylbenzylcarbonyl)piperazine

Compound **5b** is prepared according to the same procedure as that described for compound **2b** from the following reagents: compound **5a** (765 mg, 2.4 mmol); trifluoroacetic acid (2.2 ml), dichloromethane (12 ml). The crude product is purified by flash chromatography with a (95/5/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 436 mg (Yield: 83%)

Elemental analysis for: $C_{14}H_{18}N_2O$

Calculated values: C 69.80; H 8.38; N 12.52; *Experimental*

values: C 69.93; H 8.44; N 12.44

1H NMR (CDCl$_3$): 2.26 (s,3H); 2.71 (t,4.8Hz,2H); 2.83 (t,5.1Hz,2H); 3.37 (t,5.0Hz,2H); 3.64 (t,5.1Hz,2H); 3.66 (s,2H); 4.75 (s,1H); 7.14 (m,4H).

Compound 5c : **1-chlorocarbonyl-4-(2-methylbenzyl-carbonyl)piperazine**

A solution of compound **5b** (300 mg, 1.37 mmol) and of pyridine (110 ml, 1.37 mmol) in dichloromethane (10 ml) is slowly delivered by a cannula-like tube over a solution of triphosgene (136 mg, 0.46 mmol) in dichloromethane (10 ml) kept at 0°C. The mixture is then brought to room temperature and left for 1/2 h before being diluted with water. The organic phase is then washed with a saturated sodium chloride solution, dried over magnesium sulfate and concentrated. The crude product is purified by flash chromatography with a (40/60) petroleum ether/ethyl acetate mixture.

Mass obtained : 261 mg (Yield: 67%)

IR (KBr) : 2923,2890,1721,1643

1H NMR (CDCl$_3$) : 2.26 (s,3H); 3.45-3.71 (M,8H); 3.68 (s,2H); 7.12 (m,4H).

Compound 5 : A solution of 4-chloro-3-(4-methyl-piperazin-1-yl)phenol prepared according to the method described in French Patent No. 9408981 (211 mg, 0.93 mmol) in tetrahydrofuran (4 ml) is delivered by a cannula-type tube over a sodium hydride suspension (50%, 49 mg, 1.02 mmol) in tetrahydrofuran (10 ml) kept at 0°C. The reaction mixture is then brought to room temperature and stirred for 20 min. After this time, a solution of compound **5c** (261 mg, 0.93 mmol) is added and the mixture is stirred for a further 1 h. It is diluted with water and extracted three times with ethyl acetate. The

combined organic phases are washed with a saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated. The crude product is purified by flash chromatography with a (95/5/1) dichloromethane/ methanol/ammonium hydroxide mixture.

Mass obtained : 394 mg (Yield: 90%)

This compound is dissolved in methanol and treated with fumaric acid to give the corresponding fumarate. The latter is crystallized from ether.

Elemental analysis for: $C_{35}H_{43}ClN_4O_4 \cdot C_4H_4O_4$
Calculated values: C 59.33 ; H 6.01 ; N 9.54 ;
Experimental values: C 59.43 ; H 6.05 ; N 9.56

Mass (DCI/NH3) : 471(MH+),437,339,219,136

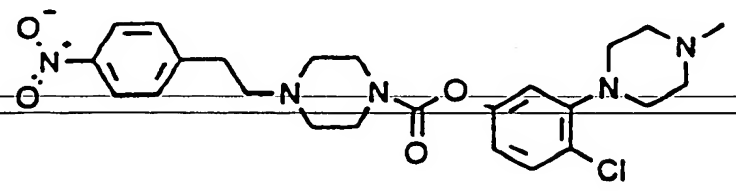
IR (KBr): 3450,3009,2927,2853,1698,1646,1428,1242

1H NMR (DMSO): 2.21 (s,3H); 2.33 (s,3H); 2.63 (M,4H); 3.01 (M,4H); 3.45 (M,2H); 3.60 (M,6H); 3.74 (s,2H); 6.60 (s,2H); 6.85 (dd, 2.7 and 8.7 Hz,1H); 6.95 (d,2.6 Hz,1H); 7.07-7.16 (m,4H); 7.41 (d,8.6 Hz,1H).

Melting point: 189°C

EXAMPLE 6

4-[Chloro-3-(4-methylpiperazin-1-yl)]phenyl 4-(4-nitrophenethyl)piperazin-1-yloate hemifumarate



Compound 6a : 1-(4-nitrophenethyl)piperazine

A solution of 4-nitrophenethyl bromide (1.58 g; 6.52 mmol) is stirred for two hours at room temperature in the presence of piperazine (2.81 g; 32.6 mmol) and of cesium carbonate (3.19 g; 9.8 mmol) in DMF (60 ml). The reaction mixture is then concentrated and then taken up in water and extracted three times with ethyl acetate. The organic phases are combined, washed with a saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated. The crude reaction product is purified by flash chromatography with a (95/5/1) to (85/15/1) dichloromethane/methanol/ammonium hydroxide gradient.

Mass obtained : 1.046 g (Yield: 68%)

Elemental analysis for: $C_{12}H_{17}N_3O_2$
Calculated values: C 61.26; H 7.28; N 17.86;
Experimental values: C 61.10; H 7.27; N 17.53

IR (KBr): 3266,2950,2815,1516,1344

1H NMR ($CDCl_3$): 1.85 (s, 1H), 2.47 (m, 4H), 2.56 (m, 2H), 2.87 (m, 6H), 7.33 (d, 8.6Hz, 2H), 8.11 (d, 8.7Hz, 2H).

Compound 6b : 1-chlorocarbonyl-4-(p-nitrophenethyl)-piperazine

Compound **6b** is prepared according to the procedure described for compound **5c** from the following products: 1-(4-nitrophenethyl)piperazine (397 mg, 1.69 mmol), triphosgene (168 mg, 0.57 mmol), pyridine (137 ml, 1.69 mmol), dichloromethane (30 ml). The crude reaction product is purified by flash chromatography with a 100/1 dichloromethane/ammonium hydroxide and then (95/5/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained : 216 mg (Yield: 43%)

IR (KBr) : 2940,2810,1730,1508,1340

Mass : 298 (MH+).

^{1}H NMR (CDCl$_3$) : 2.57 (M, 4H), 2.69 (t,7.4Hz, 2H), 2.93 (t.7.4Hz,2H), 3.67 (M, 2H), 3.76 (M, 2H), 7.37 (d,8.6Hz, 2H,), 8.16 (d,8.6Hz, 2H).

Compound 6 :

Compound **6** is prepared according to the procedure described for compound **5** from the following reagents: 4-chloro-3-(4-methylpiperazin-1-yl)phenol (148 mg, 0.66 mmol), compound **6b** (195 mg, 0.66 mmol), sodium hydride (50%, 34.6 mg, 0.72 mmol), THF (17 ml). The crude reaction product is purified by flash chromatography with a (95/5/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained : 273 mg (Yield : 85%).

Elemental analysis for $C_{23}H_{23}ClN_5O_4$-0.5$C_4H_4O_4$-0.2H_2O calculated C 56.78 H 5.94 N 12.73 Cl 6.45 ; experimental C 56.79 H 5.89 N 12.28 Cl 6.22.

Mass (DCI/NH3) : 488 (MH+).

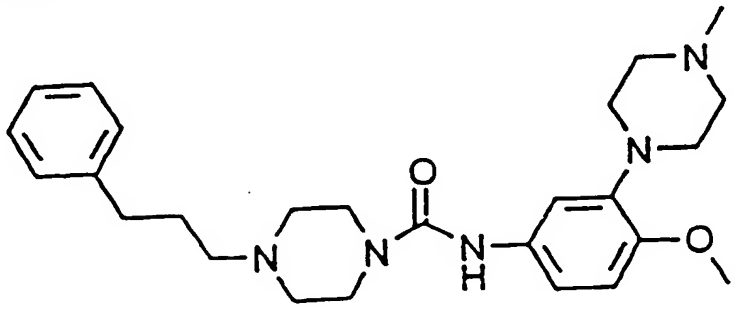
IR (KBr) : 2924,2834,1789,1518,1342.

^{1}H NMR (DMSO): 2.28 (s,3H), 2.5 (m,8H), 2.63 (d,7.7Hz,2H), 2,92 (t,7.6Hz,2H), 2.96 (M,4H), 3.42 (M,2H), 3.55 (M,2H), 6.60 (s,1H), 6.82 (dd,2.6 and 8.6Hz,1H), 6.90 (d,2.6Hz,1H), 7.39 (d,8.5Hz,1H), 7.55 (d,8.7Hz, 2H), 8.16 (d, 8.7Hz, 2H).

Melting point : 184°C.

EXAMPLE 7

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-(3-phenylpropan-1-yl)piperazin-1-ylamide fumarate



7

Compound 7a : N-[4-methoxy-3-(4-methylpiperazin-1-yl)-phenyl]-4-tert-butyloxycarbonylpiperazin-1-ylamide

Compound **7a** is prepared according to the procedure described in Example **1** from the following reagents : triphosgene (2.21 g, 7.75 mmol); 4-methoxy-3-(4-methyl-piperazin-1-yl)aniline (4.94 g, 22.36 mmol); pyridine (1.81 ml×2, 22.36 mmol×2); 1-(tert-butyloxycarbonyl)-piperazine (4.16 g, 22.36 mmol); dichloromethane (200 ml).

Mass obtained : 9.55 g (crude yield: 99%)

1H NMR ($CDCl_3$) : 1.43 (s,9H); 2.55 (s,3H); 2.90 (M,4H); 3.16 (M,4H); 3.42 (M,8H); 3.77 (s,3H); 6.71 (d,10.1Hz,1H); 6.93 (d,2.3Hz,1H); 7.18 (m,1H); 7.44 (s,1H).

Compound 7b: N-[4-methoxy-3-(4-methylpiperazin-1-yl)-phenyl]-4-piperazin-1-ylamide

Compound **7b** is prepared according to the same procedure as that described for compound **2b** from the following reagents: compound **7a** (9.55 g, 22 mmol); trifluoroacetic acid (15 ml); dichloromethane (150 ml). After neutralization of the trifluoroacetic acid, the two phases are evaporated off under reduced pressure and then the crude

product obtained is filtered on silica with a (60/40/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained : 6.06 g (Yield: 83%)

1H NMR (DMSO): 2.22 (s,3H); 2.45 (M,4H); 2.67 (M,4H); 2.93 (M,4H); 3.32 (M,4H); 3.72 (s,3H); 6.78 (d,8.6Hz,1H); 7.01-7.09 (m,2H); 8.18 (s,1H).

Compound 7 : Compound 7 is prepared according to the procedure described for compound **6a** from the following reagents: compound **7b** (587 mg, 1.76 mmol); 1-bromo-3-phenylpropane (330 ml, 2.11 mmol); cesium carbonate (860 mg, 2.64 mmol); dimethylformamide (20 ml). The crude product is purified by flash chromatography with a (91/9/1) (dichloromethane/methanol/ammonium hydroxide) mixture. Two products are isolated.

* The least polar compound : N-[4-methoxy-3-(4-methyl-piperazin-1-yl)phenyl]-4-(3-phenylpropan-1-yloxy-carbonyl)piperazin-1-ylamide

Mass obtained : 187 mg (Yield: 24%)

1H NMR ($CDCl_3$) : 1.99 (m,2H); 2.41 (M,3H); 2.71 (M,6H); 3.14 (M,4H); 3.48 (M,8H); 3.83 (s,3H); 4.14 (t,6.5Hz,2H); 6.33 (s,1H); 6.77 (d,8.6Hz,1H); 6.93-7.01 (m,2H); 7.16-7.28 (m,5H).

* The most polar compound : compound 7

Mass obtained : 300 mg (Yield: 38%)

Elemental analysis for: $C_{26}H_{37}N_5O_2$-1.2$C_4H_4O_4$-0.5H_2O
Calculated: C 61.67 ; H 7.19 ; N 11.67 ;
Experimental: C 61.54 ; H 7.57 ; N 11.69

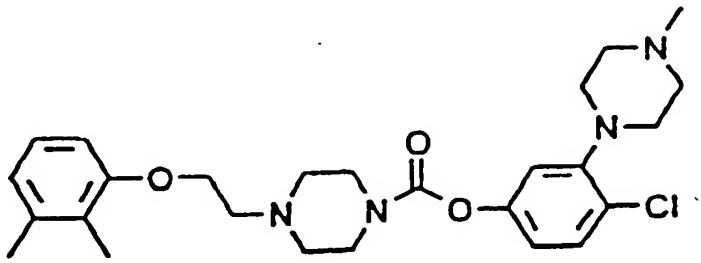
IR (KBr): 3435,3026,2938,2838,1649,1508

1H NMR (DMSO) : 1.76 (m,2H); 2.37 (M,9H); 2.56-2.68 (M,6H); 2.99 (M,4H); 3.42 (M,4H); 3.73 (s,3H); 6.58 (s,2.4H); 6.79 (d,8.7Hz,1H); 7.04-7.09 (m,2H); 7.20-7.32 (m,5H); 8.08 (s,1H).

Melting point : 164°C

EXAMPLE 8

4-[Chloro-3-(4-methylpiperazin-1-yl)]phenyl 4-[2-(2,3-dimethylphenyloxy)ethan-1-yl)piperazin-1-yloate difumarate



8

Compound 8a : 2-chloro-1-(4-*tert*-butyloxycarbonyl-piperazin-1-yl)ethanone

Chloroacetyl chloride (2.42 ml, 30.4 mmol) is added dropwise to a solution of 1-*tert*-butyloxycarbonyl-piperazine (5.15 mg, 27.6 mmol) and of calcium carbonate (8.34 g, 83.4 mmol) in methyl ethyl ketone (60 ml) cooled to 0°C. The reaction mixture is stirred at this temperature for 1h 30 min and then it is filtered on Celite. The Celite is rinsed several times with ethyl acetate and a 3 M sodium hydroxide solution. The two phases of the filtrate are then separated and the organic phase is dried over magnesium sulfate, filtered and concentrated to give the expected product.

Mass obtained : 4.07 g (Yield: 56%)

1H NMR (DMSO) : 1.41 (s,9H); 3.36-3.64 (M,8H); 4.03 (s,2H).

Compound 8b : **2-(2,3-dimethylphenyloxy)-1-(4-*tert*-butyloxycarbonylpiperazin-1-yl)ethanone**

Compound **8b** is prepared according to the procedure described for compound **6a** from the following reagents: compound **8a** (1.33 g, 5.07 mmol); 2,3-dimethylphenol (620 mg, 5.07 mmol); cesium carbonate (3.3 g, 10.1 mmol); dimethylformamide (20 ml). The mixture is stirred for 12 h. The crude product is purified by flash chromatography with a (91/9/1) (dichloromethane/methanol/ammonium hydroxide) mixture.

Mass obtained : 1.95 g (quantitative yield)

1H NMR ($CDCl_3$) : 1.41 (s,9H); 2.11 (s,3H); 2.21 (s,3H); 3.37 (M,4H); 3.52 (M,4H); 4.62 (s,2H); 6.62 (d,7.6Hz,1H); 6.75 (d,7.4Hz,1H); 6.98(t,7.8Hz,1H).

Compound 8c : **2-(2,3-dimethylphenyloxy)-1-(piperazin-1-yl)ethanone**

Compound **8c** is prepared according to the same procedure as that described for compound **2b** from the following reagents: compound **8b** (1.95 g, 5.07 mmol); trifluoroacetic acid (5.0 ml); dichloromethane (25 ml). The crude product is purified by flash chromatography with a (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained : 991 mg (Yield: 79%)

1H NMR ($CDCl_3$) : 2.18 (s,3H); 2.27 (s,3H); 2.85 (t,5.1Hz,4H); 3.60 (M,4H); 4.67 (s,2H); 6.73 (d,8.2Hz,1H); 6.81 (d,7.5Hz,1H); 7.05 (t,7.9Hz,1H).

Compound 8d : **1-(2,3-dimethylphenyloxyethan-1-yl)-piperazine**

Compound **8d** is prepared according to the procedure described for compound **3a** from the following reagents: compound **8c** (515 mg, 2.08 mmol); lithium aluminum hydride (3.1 ml of a 1 M solution in tetrahydrofuran, 3.1 mmol);

ethyl ether (10 ml). The reaction lasts for 3 h. The crude reaction product is used as it is in the next stage.

Mass obtained: 354 mg (Yield: 73%)

Compound 8e : 1-chlorocarbonyl-4-(2,3-dimethylphenyloxy-ethan-1-yl)piperazine

Compound **8e** is prepared according to the procedure described for compound **5c** from the following reagents: compound **8d** (354 mg, 1.51 mmol); triphosgene (150 mg, 0.50 mmol); pyridine (125 ml, 1.51 mmol); dichloromethane (40 ml). The crude reaction product is purified with a (99.5/0.5/0.5) to (95/5/1) dichloromethane/methanol/ammonium hydroxide gradient.

Mass obtained : 336 mg (Yield: 75%)

1H NMR ($CDCl_3$) : 2.14 (s,3H); 2.27 (s,3H); 2.66 (t,5.2Hz,4H); 2.88 (t,5.4Hz,2H); 3.64-3.77 (M,4H); 4.09 (t,5.4Hz,2H); 6.68 (d,8.1Hz,1H); 6.79 (d,7.5Hz,1H); 7.04 (t,7.8Hz,1H).

compound 8 :

Compound **8** is prepared according to the procedure described for compound **5** from the following reagents: compound **8e** (333 mg, 1.12 mmol); 4-chloro-3-(4-methyl-piperazin-1-yl)phenol (255 mg, 1.12 mmol); sodium hydride (50%, 50 mg, 1.12 mmol); tetrahydrofuran (20 ml). The crude reaction product is purified with a (95/5/1) and then (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained : 379 mg (Yield: 70%)

Elemental analysis for: $C_{26}H_{35}ClN_4O_3 \cdot 2C_4H_4O_4 \cdot 0.65H_2O$

Calculated: C 55.87 ; H 6.11 ; N 7.67 ;

Experimental: C 55.63 ; H 6.10 ; N 7.58

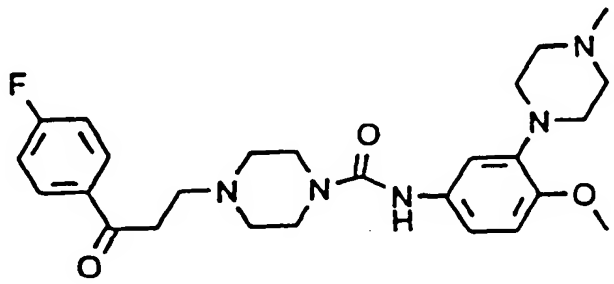
IR (KBr): 3434,2940,1722,1591,1255

1H NMR (DMSO) : 2.09 (s,3H); 2.2 (s,3H); 2.37 (s,3H); 2.2.60 (M,4H); 2.67 (M,4H); 2.81 (t,5.5Hz,2H); 3.03 (M,4H); 3.45 (M,2H); 3.59 (M,2H); 4.08 (t,5.6Hz,2H); 6.62 (s,4H); 6.74-7.07 (m,5H); 7.40 (d,8.5Hz,1H).

Melting point: 85°C

EXAMPLE 9

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-[3-(4-fluorophenyl)-3-oxopropan-1-yl)piperazin-1-ylamide fumarate



9

A solution of 3-chloro-4-fluoropropiophenone (340 mg; 1.8 mmol) is stirred for 5 h at room temperature in the presence of N-[4-methoxy-3-(4-methylpiperazin-1-yl)-phenyl]-4-piperazin-1-ylamide (**7b**) (500 mg; 1.5 mmol), potassium carbonate (310 mg; 2.25 mmol) and potassium iodide (a spatula tip) in methyl ethyl ketone (20 ml). The reaction mixture is then poured into water and extracted three times with ethyl acetate. The organic phases are combined, washed with a saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated. The crude reaction product is purified by flash chromatography with a (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 440 mg (Yield: 76%)

Elemental analysis for: $C_{26}H_{34}FN_5O_3 \cdot C_4H_4O_4 \cdot 0.45H_2O$

Calculated values: C 59.29; H 6.45; N 11.52;
Experimental values: C 59.16; H 6.42; N 11.34

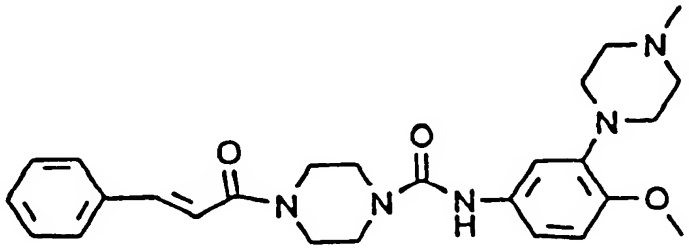
IR (KBr): 3435,3314,2838,1689,1602,1508

1H NMR (DMSO): 2.33 (s,3H); 2.43 (M,4H); 2.62 (M,4H); 2.70 (t,7.0H,2H); 2.96 (M,4H); 3.23 (t,7.1Hz,2H); 3.39 (M,4H); 3.71 (s,3H); 6.57 (s,2H); 6.78 (d,8.7Hz,1H); 7.02-7.08 (m,2H); 7.35 (t,8.8Hz,2H); 8.07 (dd,5.5 and 8.8Hz,2H); 8.27 (s,1H).

Melting point: 132°C

EXAMPLE 10

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-[(E)-styrylcarbonyl]piperazin-1-ylamide fumarate



10

Compound **10** is prepared according to the procedure described for compound **2a** from the following reagents: compound **7b** (500 mg, 1.5 mmol); cinnamic acid (220 mg, 1.5 mmol); 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (290 mg, 1.5 mmol); 4-dimethylaminopyridine (a spatula tip); dichloromethane (15 ml). The reaction lasts for 5 h. The crude reaction product is purified by flash chromatography with a (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 414 mg (Yield: 60%)

Elemental analysis for: $C_{26}H_{31}N_5O_3 \cdot C_4H_4O_4 \cdot 0.27H_2O$
Calculated values: C 61.65; H 6.47; N 11.98;
Experimental values: C 61.56; H 6.65; N 11.80

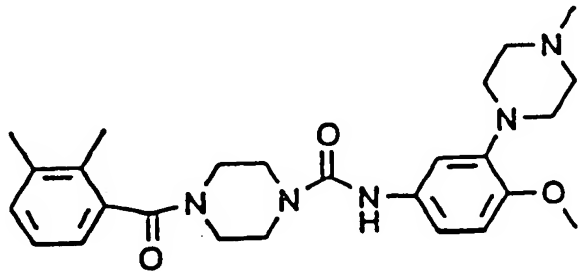
IR (KBr): 3395,3005,2831,1702,1642

1H NMR (DMSO): 2.39 (s,3H); 2.70 (M,4H); 3.02 (M,4H); 3.41 (M,4H); 3.63 (M,2H); 3.75 (M,5H); 6.59 (s,2H); 6.83 (d,8.6Hz,1H); 7.07-7.12 (M,2H); 7.28-7.59 (M,5H); 7.77 (M,2H); 8.43 (s,1H).

Melting point : 180°C

EXAMPLE 11

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-(2,3-dimethylphenylcarbonyl]piperazin-1-ylamide fumarate



11

Compound **11** is prepared according to the procedure described for compound **2a** from the following reagents: compound **7b** (500 mg, 1.5 mmol); 2,3-dimethylbenzoic acid (220 mg, 1.5 mmol); 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (290 mg, 1.5 mmol); 4-dimethylaminopyridine (a spatula tip); dichloromethane (20 ml). The reaction lasts for 2 h. The crude reaction product is purified by flash chromatography with a (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 479 mg (Yield: 68%)

Elemental analysis for: $C_{26}H_{35}N_5O_3-C_4H_4O_4-0.3H_2O$

Calculated values: C 61.38; H 6.80; N 11.93;

Experimental values: C 61.31; H 6.97; N 11.58

IR (KBr): 3422,2918,2838,1709,1635,1508

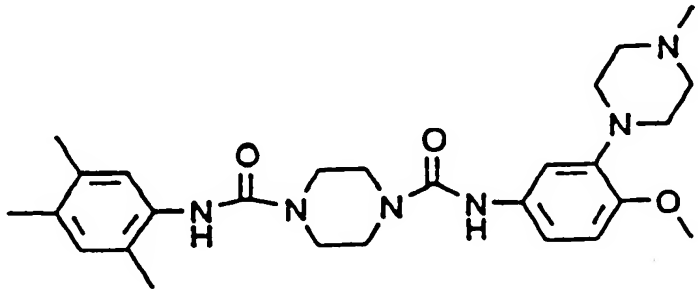
1H NMR (DMSO): 2.10 (s,3H); 2.25 (s,3H); 2.38 (s,3H);

2.70 (M,4H); 2.98(M,4H); 3.11 (M,2H); 3.31 (M,2H); 3.51 (M,2H); 3.68 (M,2H); 3.71 (s,3H); 6.55 (s,2H); 6.78 (d,8.7Hz,1H); 6.98-7.21 (m,5H); 8.38 (s,1H).

Melting point: 185°C

EXAMPLE 12

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-(2,4,5-trimethylphenylaminocarbonyl]piperazin-1-ylamide fumarate



12

Compound **12** is prepared according to the procedure described for compound **1** from the following reagents: compound **7b** (500 mg, 1.5 mmol); 2,4,5-trimethylaniline (200 mg, 1.5 mmol); triphosgene (160 mg, 0.55 mmol); pyridine (130 ml×2, 1.65 mmol×2); dichloromethane (30 ml). The crude reaction product is purified by flash chromatography with a (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 376 mg (Yield: 51%)

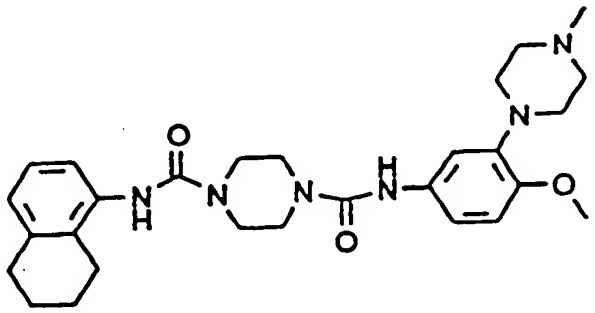
Elemental analysis for: $C_{27}H_{38}N_6O_3$-$C_4H_4O_4$
Calculated values: C 60.97; H 6.93; N 13.76;
Experimental values: C 60.86; H 7.06; N 13.75

IR (KBr): 3301,2918,2838,1635,1510
1H NMR (DMSO): 2.10 (s,6H); 2.22 (s,3H); 2.36 (s,3H); 2.67 (M,4H); 2.99 (M,4H); 3.46 (M,8H); 3.73 (s,3H); 6.58 (s,2H); 6.81 (d,8.7Hz,1H); 6.85 (s,2H); 7.05-7.11 (m,2H); 7.86 (s,1H); 8.36 (s,1H).

Melting point: 245°C

EXAMPLE 13

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-(5,6,7,8-tetrahydronaphthylaminocarbonyl]piperazin-1-ylamide fumarate



13

Compound **13** is prepared according to the procedure described by compound **1** from the following reagents: compound **7b** (604 mg, 1.81 mmol); 5,6,7,8-tetrahydronaphthylamine (301 mg, 2.0 mmol); triphosgene (202 mg, 0.68 mmol); pyridine (162 ml×2, 1.81 mmol×2); dichloromethane (60 ml). The crude reaction product is purified by flash chromatography with a (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 678 mg (Yield: 74%)

Elemental analysis for: $C_{29}H_{38}N_6O_3 \cdot C_4H_4O_4 \cdot 0.55H_2O \cdot 0.4C_4H_{10}O$
Calculated values: C 60.94; H 7.17; N 12.69;
Experimental values: C 60.97; H 7.44; N 12.59

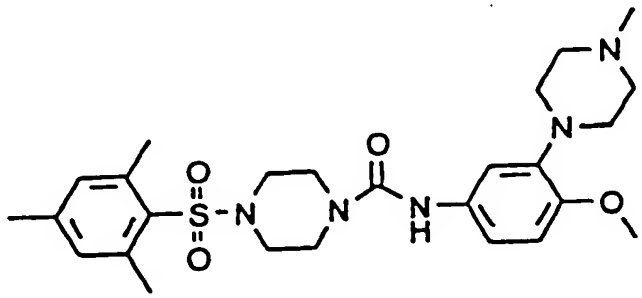
IR (KBr): 3295,2932,2851,1642,1508

1H NMR (DMSO): 1.67 (M,4H); 2.30 (s,3H); 2.59 (M,6H); 2.70 (M,2H); 2.95 (M,4H); 3.43 (M,8H); 3.71 (s,3H); 6.56 (s,2H); 6.79 (d,8.7Hz,1H); 6.87 (m,1H); 6.98-7.08 (m,4H); 7.95 (s,1H); 8.33 (s,1H).

Melting point: 144°C

EXAMPLE 14

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-(2,4,6-trimethylbenzenesulfonyl)piperazin-1-ylamide fumarate



14

A solution of mesytilene sulfonide chloride (650 mg, 2.97 mmol) in dichloromethane (5 ml) is added to a solution of compound **7b** (500 mg, 1.50 mmol) in 1 M sodium hydroxide (1.1 ml) at 0°C. The biphasic mixture is then brought to room temperature and stirred for 5 h. After this time, the two phases are separated and the aqueous phase is extracted three times with dichloromethane. The combined organic phases are washed with a saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated. The crude reaction product is purified by flash chromatography with a (95/5/1) and then (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 330 mg (Yield: 43%)

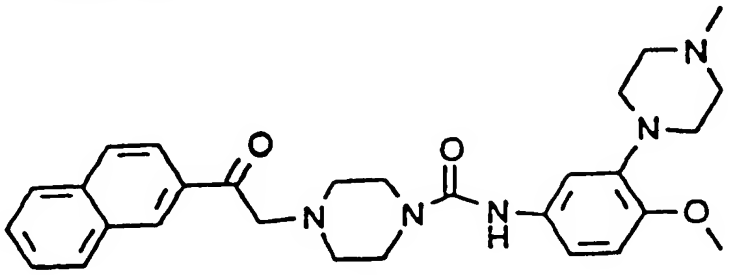
Elemental analysis for: $C_{36}H_{47}N_5O_4S\text{-}C_4H_4O_4$
Calculated values: C 57.04; H 6.54; N 11.09;
Experimental values: C 56.85; H 6.69; N 10.91

IR (KBr): 3402, 2938, 2851, 1642, 1508
1H NMR (DMSO): 2.28 (s,3H); 2.35 (s,3H); 2.56 (s,6H); 2.62 (M,4H); 3.01 (M,8H); 3.45 (M,4H); 3.71 (s,3H); 6.57 (s,2H); 6.79 (d,8.7Hz,1H); 6.98-7.16 (2H); 7.10 (s,2H); 8.40 (s,1H).

Melting point: 175°C

EXAMPLE 15

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-(2-naphthyl-2-oxoethan-1-yl)piperazin-1-ylamide fumarate



15

Compound 15a : (piperazin-1-yl)methyl-2-naphthyl ketone

The compound **15a** is prepared according to the procedure described for compound **6a** from the following reagents: bromomethyl-2-naphthyl ketone (5 g, 20 mmol); piperazine (8.6 g, 2.100 mmol); cesium carbonate (9.8 g, 30 mmol); dimethylformamide (200 ml). The crude product is purified by flash chromatography with an (85/15/1) and then (80/18/2) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 1.03 g (Yield: 20.2%)

1H NMR ($CDCl_3$): 2.64 (M,4H); 2.97 (M,4H); 3.92 (s,2H); 7.58 (m,2H); 7.83-8.03 (m,4H); 8.52 (s,1H).

Compound 15 :

Compound **15** is prepared according to the procedure described for compound **1** from the following reagents: compound **15a** (588 mg, 2.31 mmol); 4-methoxy-3-(4-methyl-piperazin-1-yl)aniline (490 mg, 2.31 mmol); triphosgene (250 mg, 0.84 mmol); pyridine (200 ml×2, 2.53 mmol×2); dichloromethane (50 ml). The crude reaction product is purified by flash chromatography with a (95/5/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 248 mg (Yield: 21%)

Elemental analysis for: $C_{24}H_{31}N_5O_2-C_4H_4O_4-H_2O$
Calculated values: C 62.35 ; H 6.50 ; N 11.02 ;
Experimental values: C 63.03 ; H 6.47 ; N 11.19

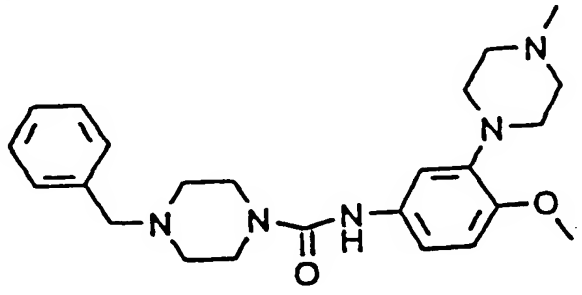
IR (KBr): 3395,2925,2838,1514,1232

1H NMR (DMSO): 2.33 (s,3H); 2.60 (M,8H); 2.96 (M,4H); 3.44 (M,4H); 3.70 (s,3H); 4.05 (s,2H); 6.56 (s,2H); 6.78 (d,8.7Hz,1H); 7.04 (m,2H); 7.64 (m,2H); 7.99 (m,2H); 8.10 (m,1H); 8.27 (s,1H); 8.70 (s,1H).

Melting point: 123°C

EXAMPLE 16

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-benzyl-piperazin-1-ylamide fumarate



16

Compound **16** is prepared according to the procedure described for compound **1** from the following reagents: 4-methoxy-3-(4-methylpiperazin-1-yl)aniline (457 mg, 2.07 mmol); 1-benzylpiperazine (364 mg, 2.07 mmol); triphosgene (205 mg, 0.69 mmol); triethylamine (290 ml×2, 2.07 mmol×2); dichloromethane (40 ml). The crude reaction product is purified by flash chromatography with a (95/5/1) then (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 776 mg (Yield: 89%)

Elemental analysis for: $C_{24}H_{31}N_5O_2-C_4H_4O_4-0.25H_2O$
Calculated values: C 61.81; H 6.95; N 12.87;

Experimental values: C 62.17; H 7.04; N 12.81

Mass (DCI/NH3) : 424 (MH+),248,177,137,120

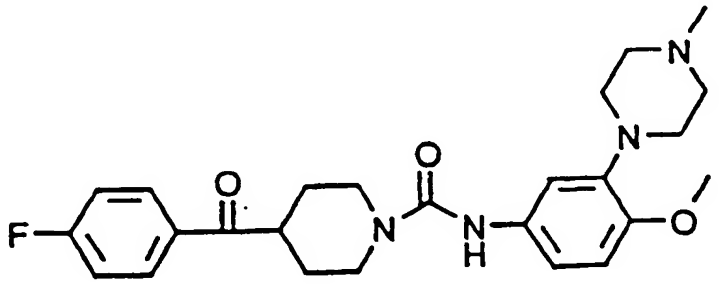
IR (KBr): 3414,2833,1637,1604,1508,1234

1H NMR (DMSO): 2.35 (M,7H); 2.65 (M,4H); 2.97 (M,4H); 3.35 (M,4H); 3.49 (s,2H); 3.71 (s,3H); 6.56 (s,2H); 6.77 (d,1H); 7.04 (m,2H); 7.30 (m,5H); 8.26 (s,1H).

Melting point: 145°C

EXAMPLE 17

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-(4-fluorobenzyl)oxopiperidin-1-ylamide fumarate



17

Compound **17** is prepared according to the procedure described for compound **1** from the following reagents: 4-methoxy-3-(4-methylpiperazin-1-yl)aniline (398 mg, 1.80 mmol); 4-fluorobenzyloxopiperidine (608 mg, 2.93 mmol); triphosgene (180 mg, 0.60 mmol); pyridine (150 ml×2, 1.80 mmol×2); dichloromethane (40 ml). The crude reaction product is purified by flash chromatography with a (95/5/1) then (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 646 mg (Yield: 79%)

Elemental analysis for: $C_{25}H_{31}FN_4O_4 \cdot C_4H_4O_4 \cdot 0.45H_2O$

Calculated values: C 60.19; H 6.25; N 9.68;

Experimental values: C 60.39; H 6.24; N 9.63

Mass (DCI/NH3) : 455(MH+),248,208

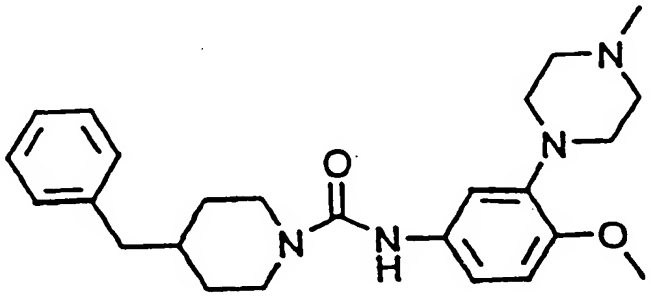
IR (KBr): 3400,2952,2838,1678,1638,1597,1233

1H NMR (DMSO): 1.10 (m,2H); 1.46 (m,2H); 2.35 (s,3H); 2.74 (M,4H); 2.98 (M,6H); 3.74 (M,4H); 4.15 (de,13Hz,2H); 6.60 (s,2H); 6.81 (d,8.6 Hz,1H); 7.06 (m,2H); 7.39 (t,8.8Hz,2H); 8.13 (m,2H); 8.30 (s,1H).

Melting point: 118°C

EXAMPLE 18

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-benzyl-piperidin-1-ylamide fumarate



18

Compound **18** is prepared according to the procedure described for compound **1** from the following reagents: 4-methoxy-3-(4-methylpiperazin-1-yl)aniline (480 mg, 2.17 mmol); benzylpiperidine (382 ml, 2.17 mmol); triphosgene (215 mg, 0.72 mmol); triethylamine (300 ml×2, 2.17 mmol×2); dichloromethane (10 ml). The crude reaction product is purified by flash chromatography with a (90/9/1) dichloromethane/methanol/ammonium chloride mixture.

Mass obtained: 780 mg (Yield: 85%)

Elemental analysis for: $C_{25}H_{34}N_4O_2 \cdot C_4H_4O_4$
Calculated values: C 64.67; H 7.11; N 10.40;
Experimental values: C 65.03; H 7.41; N 10.61

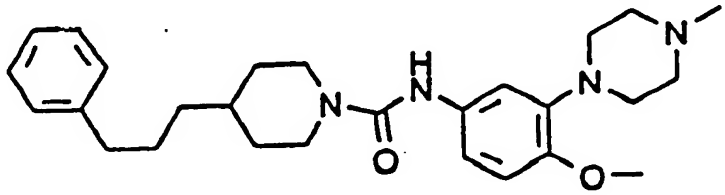
Mass (DCI/NH3) : 423 (MH+),248,176

IR (KBr): 3408,2934,2841,1707,1637,1500
1H NMR (DMSO): 1.07 (m,2H); 1.61 (m,3H); 2.34 (s,3H); 2.53 (M,2H); 2.63 (M, 6H); 2.98 (M,4H); 3.73 (s,3H); 4.06 (M,2H); 6.59 (s,2H); 6.79 (d,8.7 Hz,1H); 7.02-7.34 (m,7H); 8.22 (s,1H).

Melting point: 160°C

EXAMPLE 19

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-(3-phenylpropan-1-yl)piperidin-1-ylamide fumarate



19

Compound 19 is prepared according to the procedure described for compound 1 from the following reagents: 4-methoxy-3-(4-methylpiperazin-1-yl)aniline (516 mg, 2.33 mmol); 4-(3-phenylpropan-1-yl)piperidine (473 mg, 2.33 mmol); triphosgene (231 mg, 0.78 mmol); triethylamine (330 ml×2, 2.33 mmol×2); dichloromethane (40 ml). The crude reaction product is purified by flash chromatography with a (94/6/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 712 mg (Yield: 68%)

Elemental analysis for: $C_{27}H_{38}N_4O_2 \cdot 2C_4H_4O_4$
Calculated values: C 61.57; H 6.79; N 8.21;
Experimental values: C 61.65; H 6.90; N 8.37

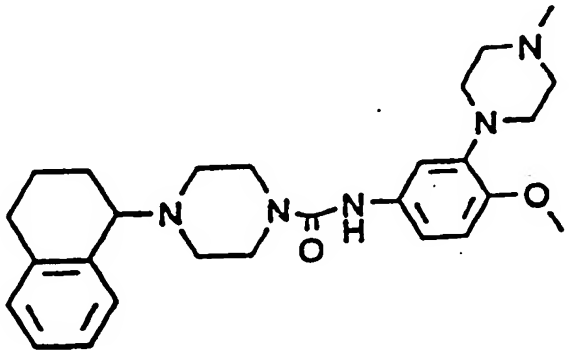
Mass (DCI/NH3): 451 (MH+),248,204,136

IR (KBr): 3384,3025,2930,2849,1709,1504

1H NMR (DMSO): 0.88-1.65 (m,9H); 2.38 (s,3H); 2.50 (m,2H); 2.72 (M,6H); 2.98 (M,4H); 3.69 (s,3H); 4.00 (M,1H); 4.07 (M,1H); 6.55 (s,4H); 6.75 (d,8.6 Hz,1H); 7.01-7.28 (m,7H); 8.17 (s,1H).

EXAMPLE 20

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-(1,2,3,4-tetrahydronaphthyl-1-)piperazin-1-ylamide fumarate



20

Compound 20a : 1-(1,2,3,4-tetrahydronaphthyl)piperazine

A solution of 1,2,3,4-tetrahydronaphthylamine (6 ml, 41.8 mmol) and of bis(2-chloroethyl)amine hydrochloride (7.44 g, 41.8 mmol) in the presence of sodium carbonate (2.22 g, 20.9 mmol) in 1-butanol is heated under reflux for 48 h. After this time, the 1-butanol is evaporated off under reduced pressure and the crude reaction product is impregnated on silica and then purified by flash chromatography with a (98/2/1) to (80/20/1) dichloromethane/methanol/ammonium hydroxide gradient.

Mass obtained : 386 mg (Yield: 4.3%)

1H NMR (CDCl$_3$) : 1.66 (m,2H); 1.93 (m,2H); 2.40-2.97 (M,10H); 3.74 (M,1H); 6.99-7.17 (m,3H); 7.68 (M,1H).

Compound 20 :

Compound 20 is prepared according to the procedure described for compound 1 from the following reagents:

4-methoxy-3-(4-methylpiperazin-1-yl)aniline (375 mg, 1.70 mmol); compound **20a** (380 mg, 1.76 mmol); triphosgene (168 mg, 00.57 mmol); triethylamine (235 ml×2, 1.70 mmol×2); dichloromethane (40 ml). The crude reaction product is purified by flash chromatography with a (95/5/1) and then (90/9/1) dichloromethane/methanol/ ammonium hydroxide mixture.

Mass obtained: 470 mg (Yield: 60%)

Elemental analysis for: $C_{27}H_{37}N_5O_2-C_4H_4O_4-0.35H_2O$
Calculated values: C 63.54; H 7.17; N 11.95;
Experimental values: C 63.64; H 7.23; N 12.09

Mass (DCI/NH3): 464(MH+),248,217,136

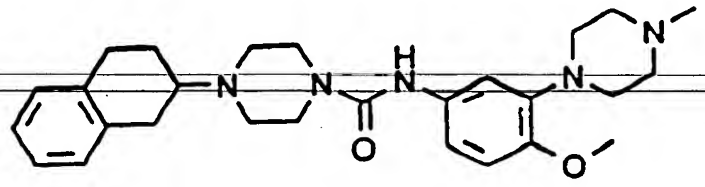
IR (KBr): 3395,2932,2835,1707,1637,1604,1506,1232

1H NMR (DMSO): 1.62 (m,2H); 1.91 (m,2H); 2.35 (s,3H); 2.51 (M,4H); 2.67 (M,6H); 2.98 (M,4H); 3.44 (M,4H); 3.73 (s,3H); 3.84 (M,1H); 6.59 (s,2H); 6.80(d,8.6Hz,1H); 7.12 (m, 5H); 7.63 (m,1H); 8.27 (s,1H).

Melting point: 110-111°C

EXAMPLE 21

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-(1,2,3,4-tetrahydronaphthyl-2)piperazin-1-ylamide fumarate



21

Compound 21a : 2-(1,2,3,4-tetrahydronaphthyl)piperazine

A solution of b-tetralone (970 mg, 6.6 mmol) and of

piperazine (2.85 mg, 33.0 mmol) in toluene (30 ml) is heated under reflux in the presence of para-toluenesulfonic acid (spatula tip) with azeotropic distillation of the water. After 48 h, the reaction mixture is cooled and diluted with ethanol (30 ml). It is then placed under hydrogen pressure (45 PSI) in the presence of platinum oxide (116 mg). After 7 h, the mixture is filtered on Celite, concentrated under reduced pressure and purified by flash chromatography with a (95/5/1) to (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 970 mg (Yield: 68%)

Mass (DCI/NH3) : 217 (MH+),177,148,132,110

1H NMR ($CDCl_3$): 1.65 (m,1H); 2.10 (M,2H); 2.63-2.97 (M,13H); 7.09 (s,4H).

Compound 21 :

Compound **21** is prepared according to the procedure described for compound **1** from the following reagents: 4-methoxy-3-(4-methylpiperazin-1-yl)aniline (665 mg, 3.00 mmol); compound **21a** (680 mg, 3.15 mmol); triphosgene (297 mg, 3.00 mmol); triethylamine (243 ml×2, 3.00 mmol×2); dichloromethane (50 ml). The crude reaction product is purified by flash chromatrography with a (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 931 mg (Yield: 67%)

Elemental analysis for: $C_{27}H_{37}N_5O_2 \cdot 1.2C_4H_4O_4 \cdot H_2O$

Calculated values: C 61.51; H 7.11; N 11.28;

Experimental values: C 61.45; H 6.79; N 10.94

Mass (DCI/NH3) : 464 (MH+),248,217,180,136

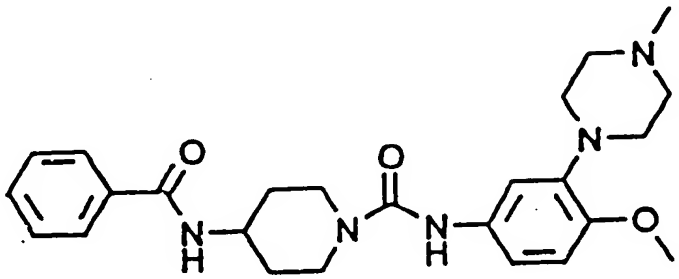
IR (KBr): 3301,2932,2844,1663,1508,1239

1H NMR (DMSO): 1.60 (M,1H); 1.99 (M,1H); 2.35 (s,3H); 2.56-2.67 (M,13H); 2.97 (M,4H); 3.40 (M,4H); 3.70 (s,3H); 6.56 (s,2.4H); 6.78 (d,8.7Hz,1H); 7.05 (M,6H); 8.27 (s,1H).

Melting point: 168-170°C

EXAMPLE 22

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-phenylcarboxamidopiperidin-1-ylamide



22

Compound 22a : 1-benzyl-4-phenylcarboxamidopiperidine

1-Benzyl-4-aminopiperidine dihydrochloride monohydrate (9 g, 34 mmol) is desalified and then dissolved in dichloromethane (70 ml) in the presence of triethylamine (7.13 ml, 51 mmol). It is cooled on an ice bath and then benzoyl chloride (3.74 ml, 40 mmol) is slowly added. The reaction mixture is then brought to room temperature, stirred for 10 min and then poured over an ice bath. The pH of the aqueous phase is brought to ~11 with a dilute sodium hydroxide solution and then the phases are separated. The organic phase is washed with a saturated sodium chloride solution before being dried over magnesium sulfate, filtered and concentrated.

Mass obtained: 8.8 g (gross yield: 88%)

1H NMR (CDCl3): 1.46 (m,2H); 2.01 (M,2H); 2.17 (td,2.3 and 11.6Hz,2H); 2.85 (M,2H); 3.51 (s,2H); 4.012 (m,1H); 6.00 (de,1H); 7.31 (M,6H); 7.48 (M,2H); 7.73 (dd,1.4 and

5.6Hz,2H).

Compound 22b : 4-phenylcarboxamidopiperidine

Compound **22a** (3.55 g, 12 mmol) dissolved in methanol (160 ml) is placed under a hydrogen pressure (40 PSI) in the presence of palladium hydroxide and acetic acid (20 ml) for 4 h. The reaction mixture is then filtered on Celite and concentrated. The oil obtained is dissolved in dichloromethane and washed three times with a 4 M sodium hydroxide solution. The organic phase is dried over magnesium sulfate, filtered and concentrated.

Mass obtained: 1.13 g (gross yield: 46%)

1H NMR ($CDCl_3$) : 1.46 (m,2H); 2.05 (M,2H); 2.76 (td,2.4 and 12.1Hz,2H); 3.17 (M,2H); 4.10 (m,1H); 6.17 (de,1H); 7.44 (M,3H); 7.75 (dd,1.5 and 7.5Hz,2H).

Compound 22 :

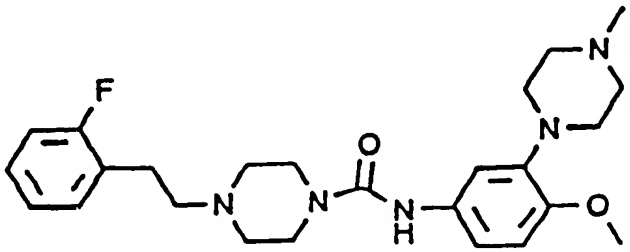
Compound **22** is prepared according to the procedure described for compound **1** from the following reagents: 4-methoxy-3-(4-methylpiperazin-1-yl)aniline (433 mg, 1.96 mmol); compound **22b** (400 mg, 1.96 mmol); triphosgene (210 mg, 0.72 mmol); pyridine (170 ml×2, 2.15 mmol×2); dichloromethane (60 ml). The crude reaction product is purified by flash chromatography with a (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 353 mg (Yield: 40%)

1H NMR ($CDCl_3$): 1.46 (m,2H); 2.10 (m,2H); 2.34 (s,3H); 2.61 (M,4H); 3.12 (M,6H); 3.82 (s,3H); 4.18 (de,2H); 4.22 (M,1H); 6.03 (d,7.7Hz,1H); 6.28 (s,1H); 6.75 (d,9.4Hz,1H); 6.95 (m,2H); 7.45 (m,3H); 7.75 (dd,1.8 and 6.0Hz,2H).

EXAMPLE 23

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-(2-fluorophenethyl)piperazin-1-ylamide fumarate



23

Compound 23a : 1-(2-fluorobenzylcarbonyl-4-(tert-butyl-oxycarbonyl)piperazine

Compound **23a** is prepared according to the same procedure as that described for compound **2a** from the following reagents: (2-fluorophenyl)acetic acid (5.50 g, 35.7 mmol); 1-*tert*-butyloxycarbonylpiperazine (6.65 g, 35.7 mmol); 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (6.84 g, 35.7 mmol); 4-dimethylamino-pyridine (a spatula tip); dichloromethane (100 ml). The crude reaction product is purified by flash chromatography with a (95/5/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained : 9.50 g (Yield: 83%)

1H NMR (CDCl$_3$) : 1.47 (s,9H); 3.31-3.47 (M,6H); 3.62 (M,2H); 3.75 (s,2H); 7.02-7.34 (m,4H).

Compound 23b: 1-(2-fluorobenzylcarbonyl)piperazine

Compound **23b** is prepared according to the same procedure as that described for compound **2b** from the following reagents: compound **23a** (9.49 g, 29.5 mmol); trifluoro-acetic acid (20 ml), dichloromethane (200 ml). The crude product is purified by flash chromatography with a (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained : 4.63 g (Yield: 71%)

1H NMR ($CDCl_3$) : 2.69-2.82 (m,4H); 3.43 (t,5.1Hz,2H); 3.59 (t,5.1Hz,2H); 3.69 (s,2H); 6.97-7.31 (m,4H).

Compound 23c : 1-(2-fluorophenethyl)piperazine

Compound **23c** is prepared according to the same procedure as that described for compound **3a** from the following reagents: compound **23b** (3.53 g, 15.9 mmol); lithium aluminum hydride (25 ml of a 1 M solution in ethyl ether, 25 mmol); ethyl ether (50 ml). The crude product is purified by flash chromatography with a (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained : 2.43 g (Yield: 73%)

1H NMR ($CDCl_3$) : 1.86 (se,1H); 2.55 (M,6H); 2.90 (M,6H); 6.94-7.22 (m,4H).

Compound 23 : The compound **23** is obtained according to the procedure described for compound **1** from the following reagents: triphosgene (371 mg, 1.25 mmol); 4-methoxy-3-(4-methylpiperazin-1-yl)aniline (828 mg, 3.75 mmol); pyridine (305 µl×2, 3.75 mmol×2); 1-(2-fluorophenethyl)-piperazine (**23c**) (780 mg, 3.75 mmol); dichloromethane (70 ml).
The crude product is purified by flash chromatography with a (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained : 1.49 g (Yield: 87%)

This compound is dissolved in methanol and treated with fumaric acid to give the corresponding fumarate. The latter is crystallized from ether.

Elemental analysis for: $C_{25}H_{34}FN_5O_2 \cdot C_4H_4O_4 \cdot 0.3H_2O$
Calculated values: C 60.36; H 6.74; N 12.014

Experimental values: C 60.77 ; H 6.93 ; N 12.31

Mass (DCI/NH3): 456(MH+),248,209

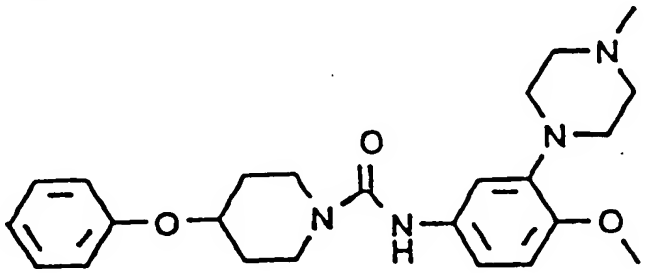
IR (KBr): 3395,2952,2831,1642,1595,1508,1232,977

1H NMR (DMSO): 2.33 (s,3H); 2.45 (M,4H); 2.51 (m,2H); 2.63 (M,4H); 2.77 (te,2H); 2.96 (M,4H); 3.39 (M,4H); 3.70 (s,3H); 6.55 (s,2H); 6.77 (d,8.7Hz,1H); 7.01-7.36 (m,6H); 8.25 (s,1H).

Melting point: 102-105°C

EXAMPLE 24

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-phenoxy-piperidin-1-ylamide fumarate



24

Compound 24a: 1-benzyl-4-phenoxypiperidine

A solution of diethyl azodicarboxylate (8.7 ml; 20.91 mmol; 40% in toluene) diluted in tetrahydrofuran (20 ml) is added dropwise to a solution of 1-benzyl-4-hydroxypiperidine (4.0 g, 20.92 mmol), phenol (1.95 g, 20.92 mmol) and triphenylphosphine (5.48 g, 20.89 mmol) in tetrahydrofuran (50 ml). The reaction mixture is stirred for 43 h and then it is poured over ice and extracted three times with ethyl acetate. The combined organic phases are then washed with a saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. The crude reaction product is impregnated over silica and then purified by flash chromatography with a (50/50/0) and then (50/50/5) petroleum

ether/ethyl acetate/ethanol mixture.

Mass obtained : 4.15 g (Yield: 74%)

1H NMR (CDCl$_3$) : 1.80 (m,2H); 1.95 (M,2H); 2.27 (M,2H); 2.72 (M,2H); 3.52 (s,2H); 4.30 (m,1H); 6.91 (M,3H); 7.28 (M,7H).

Compound 24b : 4-phenoxypiperidine

Compound **24b** is prepared according to the procedure described for compound **22b** from the following reagents: compound **24a** (4.14 g, 15.5 mmol); palladium hydroxide (300 mg); acetic acid (50 ml); methanol (160 ml). The crude reaction product is purified by flash chromatography with a (70/30/1) and then (60/40/1) petroleum ether/ethanol/ammonium hydroxide mixture.

Mass obtained : 1.35 g (Yield: 49%)

1H NMR (CDCl$_3$) : 1.69 (m,3H); 2.00 (M,2H); 2.73 (m,2H); 3.16 (m,2H); 4.37 (m,1H); 6.94 (M,3H); 7.28 (M,2H).

Compound 24 :

Compound **24** is prepared according to the procedure described for compound 1 from the following reagents: 4-methoxy-3-(4-methylpiperazin-1-yl)aniline (500 mg, 2.26 mmol); compound **24b** (400 mg, 2.26 mmol); triphosgene (225 mg, 0.76 mmol); pyridine (175 ml×2, 2.26 mmol×2); dichloromethane (50 ml). The crude reaction product is purified by flash chromatography with a (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained : 592 mg (Yield: 62%)

This compound is dissolved in methanol and treated with fumaric acid to give the corresponding fumarate. The latter is crystallized from ether.

Elemental analysis for: $C_{24}H_{32}N_4O_4 \cdot 1.1C_4H_4O_4 \cdot 0.2H_2O \cdot 0.1C_4H_{10}O$
Calculated values: C 61.42; H 6.76; N 9.95;
Experimental values: C 61.24; H 7.10; N 9.64

Mass (DCI/NH3) : 425 (MH+),280,248,192

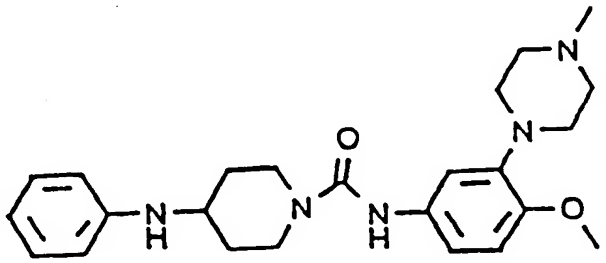
IR (KBr): 3408,2945,2838,1642,1602,1508,1232

1H NMR (DMSO): 1.55 (M,2H); 1.93 (M,2H); 2.34 (s,3H); 2.63 (M,4H); 2.98 (M,4H); 3.24 (M,2H); 3.72 (s,3H); 3.84 (m,2H); 4.58 (m,1H); 6.58 (s,1.8H); 6.80 (d,8.6Hz,1H); 6.89-7.05 (m,5H); 2.29 (m,2H); 8.33 (s,1H).

Melting point: 104°C (amorphous)

EXAMPLE 25

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-anilino-piperidin-1-ylamide fumarate



25

Compound 25a : 1-benzyl-4-anilinopiperidine

A solution of sodium cyanoborohydride (1.45 g, 23.0 mmol) in ethanol (30 ml) is added dropwise to a solution of 1-benzyl-4-piperidone (3.2 ml, 15.2 mmol), aniline (1.5 ml, 15.8 mmol) and acetic acid (1.9 ml, 25.5 mmol) in ethanol (45 ml) at room temperature. After 5 h, the reaction mixture is poured over an ice bath and it is basified with 1 N sodium hydroxide (15 ml) and extracted three times with ethyl acetate. The combined organic phases are then washed with water, dried over magnesium sulfate and concentrated. The crude reaction product is

impregnated over silica and purified by flash chromatography with a (70/50/5/1) and then (70/50/10/1) petroleum ether/ethyl acetate/ethanol/ammonium hydroxide mixture.

Mass obtained: 3.45 g (yield: 76%)

1H NMR (CDCl$_3$): 1.47 (M,2H); 2.03-2.23 (M,4H); 2.85 (M,2H); 3.32 (m,1H); 4.54 (s,2H); 6.65 (M,3H); 7.13-7.36 (M,7H).

Compound 25b: 4-anilinopiperidine

Compound **25b** is prepared according to the procedure described for compound **22b** from the following reagents: compound **25a** (3.43 g, 12.0 mmol); palladium hydroxide (440 mg); acetic acid (40 ml); methanol (160 ml). The crude reaction product is purified by flash chromatography with a (90/10) to (100/0) (dichloromethane/methanol) gradient.

Mass obtained: 1.04 g (yield: 49%)

1H NMR (CDCl$_3$): 1.33 (M,2H); 1.74 (M,1H); 2.05 (M,2H); 2.72 (m,2H); 3.11 (m,2H); 3.37 (m,1H); 3.40 M,1H); 6.63 (M,3H); 7.17 (M,2H).

Compound 25:

Compound **25** is prepared according to the procedure described for compound **1** from the following reagents: 4-methoxy-3-(4-methylpiperazin-1-yl)aniline (500 mg, 2.26 mmol); compound **25b** (400 mg, 2.26 mmol); triphosgene (225 mg, 0.76 mmol); pyridine (315 ml×2, 4.01 mmol×2); dichloromethane (50 ml). The crude reaction product is purified by flash chromatography with a (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 120 mg (yield: 12%)

This compound is dissolved in methanol and treated with fumaric acid to give the corresponding fumarate. The latter is crystallized from ether.

Elemental analysis for: $C_{24}H_{33}N_5O_2$-1.6$C_4H_4O_4$-0.5H_2O-0.4$C_4H_{10}O$ *Calculated values*: C 59.32; H 6.91; N 10.81; *Experimental values*: C 59.35; H 7.16; N 11.03

Mass (DCI/NH3): 424 (MH+),280,248,222,177

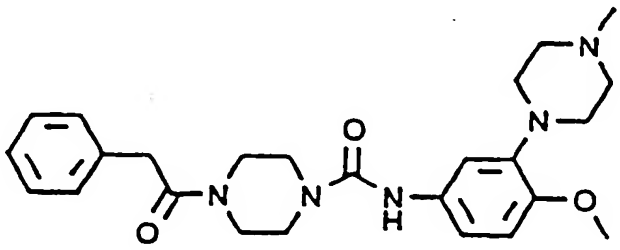
IR (KBr): 3415,2938,2838,1602,1508,1226

1H NMR (DMSO): 1.25 (M,2H); 1.90 (M,2H); 2.35 (s,3H); 2.66 (M,4H); 2.89 (M,2H); 2.96 (M,4H); 3.42 (M,1H); 3.71 (s,3H); 3.98 (M,1H); 4.06 (m,1H); 6.49 (m,2H); 6.57 (s,3.2H); 6.60 (se,1H); 6.78 (d,8.6Hz,1H); 7.01-7.09 (m,4H); 8.28 (s,1H).

Melting point: 120°C (amorphous)

EXAMPLE 26

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-(benzylcarbonyl)piperazin-1-ylamide fumarate



26

A solution of compound **7b** (630 mg, 1.89 mmol) and of phenylacetic acid (257 mg, 1.89 mmol) in dichloromethane (30 ml) is stirred for 12 h at room temperature in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimidehydrochloride (362 mg, 1.89 mmol) and 4-dimethylaminopyridine (a spatula tip). The reaction mixture is then diluted with water and then the phases are separated. The organic phase is washed with a saturated

sodium chloride solution, dried over magnesium sulfate, filtered and concentrated. The crude product is purified by flash chromatography with a (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 640 mg (yield: 75%)

This compound is dissolved in methanol and treated with fumaric acid to give the corresponding fumarate. The latter is crystallized from ether.

Elemental analysis for: $C_{25}H_{35}N_5O_3-C_4H_4O_4-0.35H_2O$

Calculated values: C 60.69; H 6.62; N 12.20;
Experimental values: C 60.21; H 6.73; N 11.92

Mass (DCI/NH3): 452 (MH+),248,205

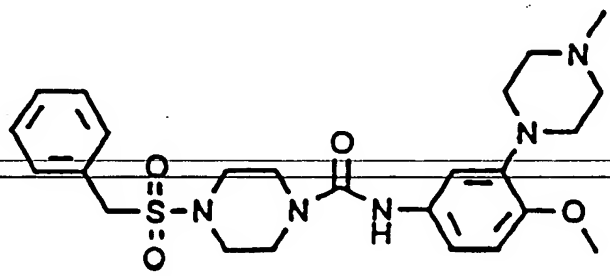
IR (KBr): 3395,3012,2925,2838,1709,1635,1508,1232,984

1H NMR (DMSO): 2.35 (s,3H); 2.65 (M,4H); 2.98 (M,4H); 3.37 (M,4H); 3.52 (M,4H); 3.73 (s,3H); 3.77 (s,2H); 6.59 (s,2H); 6.80 (d,8.7Hz,1H); 7.03-7.09 (m,2H); 7.23-7.36 (m,5H); 8.35 (s,1H).

Melting point: 118-120°C

EXAMPLE 27

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-(benzylsulfonyl)piperazin-1-ylamide fumarate



A solution of benzylsulfonyl chloride (605 mg, 3.17 mmol) in dichloromethane (5 ml) is added to a solution of compound **7b** (528 mg, 1.59 mmol) in 1 M sodium hydroxide (1.6 ml) at 0°C. The biphasic mixture is then brought to room temperature and stirred for 5 h. After this time, the two phases are separated and the aqueous phase is extracted three times with dichloromethane. The combined organic phases are washed with a saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated. The crude reaction product is purified by flash chromatography with a (95/5/1) and then (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 550 mg (yield: 71%)

This compound is dissolved in methanol and treated with fumaric acid to give the corresponding fumarate. The latter is crystallized from ether.

Elemental analysis for: $C_{24}H_{33}N_5O_4S$-0.85$C_4H_4O_4$-0.2H_2O-0.2$C_4H_{10}O$
Calculated values: C 56.01; H 6.47; N 11.58;
Experimental values: C 56.28; H 6.56; N 10.99

Mass (DCI/NH3): 488(MH+),248

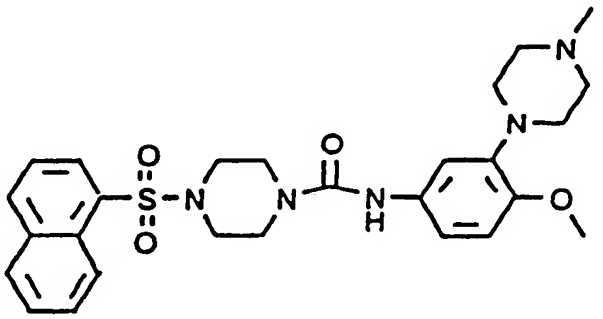
IR (KBr): 3395,2965,2925,2[illegible],1709,1642,1508,1246,1146, 984

1H NMR (DMSO): 2.36 (s,3H); 2.67 (M,4H); 2.99 (M,4H); 3.12 (M,4H); 3.43 (M,4H); 3.73 (s,3H); 4.46 (s,2H); 6.57 (s,1.7H); 6.81 (d,8.8Hz,1H); 7.01-7.08 (m,2H); 7.40 (M,5H); 8.40 (s,1H).

Melting point: 121-125°C

EXAMPLE 28

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-(1-naphthylsulfonyl)piperazin-1-ylamide fumarate



28

Compound **28** is prepared according to the procedure used for compound **27** from the following reagents: 1-naphthylsulfonyl chloride (671 mg, 296 mmol); compound **7b** (493 mg, 1.48 mmol); 1 N sodium hydroxide solution (1.5 ml); dichloromethane (5 ml). The crude reaction product is purified by flash chromatography with a (95/5/1) and then (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 756 mg (yield: 98%)

This compound is dissolved in methanol and treated with fumaric acid to give a corresponding fumarate. The latter is crystallized from ether.

Elemental analysis for: $C_{27}H_{33}N_5O_4S-C_4H_4O_4-0.2H_2O-0.15C_4H_{10}O$

Calculated values: C 57.99; H 5.99; N 10.70; *Experimental values*: C 58.14; H 5.83; N 10.80

Mass (DCI/NH3): 524 (MH+),277,248

IR (KBr): 3402,2925,2844,1702,1635,1602,1508,1239,977

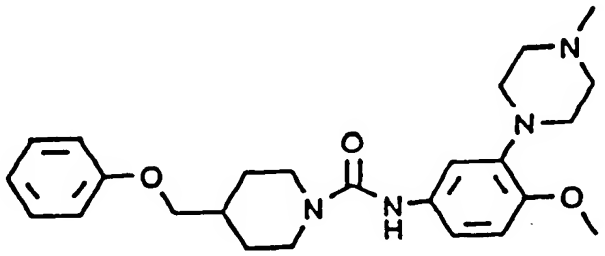
1H NMR (DMSO): 2.31 (s,3H); 2.60 (M,4H); 2.92 (M,4H); 3.08 (M,4H); 3.44 (M,4H); 3.69 (s,3H); 6.57 (s,2H); 6.75

(d,8.7Hz,1H); 6.91-6.99 (m,2H); 7.64-7.79 (m,3H); 8.11-8.18 (m,2H); 8.29-8.33 (m,2H); 8.70 (d,8.2Hz,1H).

Melting point: 110°C (amorphous)

EXAMPLE 29

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-phenoxymethylpiperidin-1-ylamide hemifumarate



29

Compound 29a: 4-phenoxymethylpiperidine

Compound **29a** is prepared according to the procedure described for compound **24a** from the following reagents: phenol (2.28 g, 24.25 mmol); 4-hydroxymethylpiperidine (2.5 g, 24.25 mmol); diethyl azodicarboxylate (11 ml; 24.25 mmol; 40% in toluene); triphenylphosphine (6.36 g, 24.25 mmol); tetrahydrofuran (70 ml). The crude reaction product is purified by flash chromatography with a (95/5/1) and then (50/50/5) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 220 mg (4.7%)

1H NMR (CDCl3): 1.30 (m,2H); 1.80-2.01 (M,4H); 2.65 (te, 11.2Hz,2H); 3.13 (de,11.9Hz,2H); 3.77 (d,6.2Hz,2H); 6.85-6.95 (m,3H); 7.22-7.30 (m,2H).

Compound 29:

Compound **29** is prepared according to the procedure described for compound **1** from the following reagents: 4-methoxy-3-(4-methylpiperazin-1-yl)aniline (255 mg,

1.15 mmol); compound **29a** (220 mg, 1.15 mmol); triphosgene (114 mg, 0.76 mmol); pyridine (90 ml×2, 1.15 mmol×2); dichloromethane (40 ml). The crude reaction product is purified by flash chromatography with a (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 225 mg (yield: 34%)

This compound is dissolved in methanol and treated with fumaric acid to give the corresponding fumarate. The latter is crystallized from ether.

Elemental analysis for: $C_{25}H_{34}N_4O_3 \cdot 0.9C_4H_4O_4 \cdot 0.35H_2O$
Calculated values: C 62.53; H 7.03; N 10.20;
Experimental values: C 62.61; H 6.96; N 10.11

Mass (DCI/NH3): 439(MH+),248,192

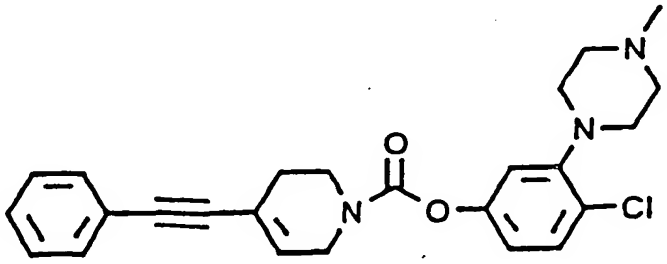
IR (KBr): 3388,2925,2838,1702,1649,1602,1508,1230

1H NMR (DMSO): 1.20 (M,2H); 1.78 (de,13.2Hz,2H), 1.96 (M,1H); 2.33 (s,3H); 2.63 (M,4H); 2.77 (te,11.8Hz,2H); 2.97 (M,4H); 3.71 (S,3H); 3.83 (d,6.2Hz,2H); 4.14 (de,13.1Hz,2H); 6.57 (s,1.8H); 6.78 (d,8.6Hz,1H); 6.91 (m,3H); 7.05 (m,2H); 7.29 (dd,7.9 and 8.9Hz,2H); 8.25 (s,1H).

Melting point: 120°C (amorphous)

EXAMPLE 30

[4-Chloro-3-(4-methylpiperidin-1-yl)]phenyl 4-phenylethynyl-1,2,3,6-tetrahydropyridin-1-yloate fumarate



30

Compound 30a: 1-benzyl-4-trifluoromethylsulfonyloxy-1,2,3,6-tetrahydropyridine

A solution of N-benzylpiperidone (9.45 ml, 53.0 mmol) in tetrahydrofuran (50 ml) is added dropwise to a solution of LDA (prepared from diisopropylamine (7.95 ml, 58.3 mmol) and of butyllithium (36.5 ml of a 1.6 M solution in hexane, 58.3 mmmmol)) in tetrahydrofuran (50 ml) at -78°C. The reaction mixture is stirred for 30 min at -78°C and then a solution of N-phenyltrifluoromethanesulfonimide (20 g, 56 mmol) in tetrahydrofuran (50 ml) is supplied by a cannula-like tube. The mixture is then brought to room temperature and stirred for 3 h before being concentrated. Finally, it is purified by rapid chromatography on a neutral alumina column with a (90/10) petroleum ether/ethyl acetate mixture.

Mass obtained: 14.2 g (83%)

1H NMR (CDCl3): 2.45 (M,2H); 2.73 (t,5.7Hz,2H); 3.13 (m,2H); 3.63 (s,2H); 5.73 (M,1H); 7.32 (M,5H).

Compound 30b: 1-benzyl-4-phenylethynyl-1,2,3,6-tetrahydropyridine

A solution of compound **30a** (6 g,18.7 mmol); phenylacetylene (3.1 ml, 28.05 mmol); triethylamine (5.1 ml,

36.9 mmol) and dichloro-*bis*-triphenylphosphinepalladium (300 mg) in dimethylformamide (75 ml) is heated at 75°C for 1 h 30 min under an argon atmosphere. After this time, the dimethylformamide is evaporated under vacuum and then the crude reaction product is taken up in water and extracted three times with ethyl acetate. The combined organic phases are then washed several times with a saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated. The crude product obtained is purified by flash chromatography with a (95/5) petroleum ether/ethyl acetate mixture.

Mass obtained: 3.38 g (yield: 66%)

1H NMR (CDCl3): 2.40 (M,2H); 2.71 (t,5.8Hz,2H); 3.17 (m,2H); 3.71 (s,2H); 6.09 (M,1H); 7.24-7.45 (M,10H).

Compound 30c: **1-chlorocarbonyl-4-phenylethynyl-1,2,3,6-tetrahydropyridine**

A solution of compound **30b** (2 g, 7.32 mmol) in dichloromethane (15 ml) is added dropwise to a solution of triphosgene (726 mg, 2.44 mmol) in dichloromethane (15 ml) at 0°C under a nitrogen atmosphere. The reaction mixture is then brought to room temperature and then stirred for 12 h. It is concentrated and then purified directly by flash chromatography with pure dichloromethane and then a (95/5/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 633 mg (yield: 36%)

1H NMR (CDCl3): 2.46 (M,2H); 3.75 (t,5.7Hz,1H); 3.84 (t,5.7Hz,1H); 4.21 (m,1H); 4.29 (m,1H); 6.07 (M,1H); 7.34 (M,3H); 7.42 (M,2H).

Compound 30:

Compound **30** is prepared according to the procedure described for compound **5** from the following reagents:

4-chloro-3-(4-methylpiperazine-1-yl)phenol (720 mg, 3.17 mmol); compound **30c** (780 mg, 3.17 mmol); sodium hydride (50%, 167 mg, 3.48 mmol); tetrahydrofuran (50 ml). The crude reaction product is purified by flash chromatography with a (90/10/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 1.1 g (yield: 80%)

This compound is dissolved in methanol and treated with fumaric acid to give the corresponding fumarate. The latter is crystallized from ether.

Elemental analysis for: $C_{25}H_{26}ClN_3O_2$-$C_4H_4O_4$
Calculated values: C 63.10; H 5.48; N 7.61;
Experimental values: C 62.84; H 5.57; N 7.44

Mass (DCI/NH3): 436 (MH+),298,227,180,136

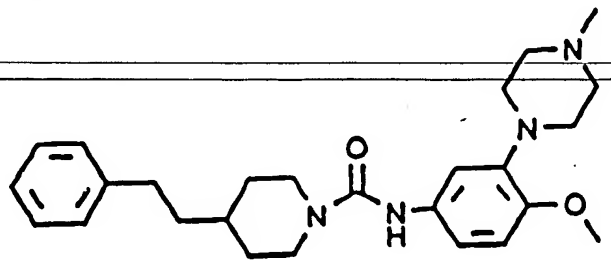
IR (KBr): 3442,2844,1723,1407

1H NMR (DMSO): 2.33 (M,5H); 2.62 (M,4H); 3.01 (M,4H); 3.57 (M,1H); 3.71 (M,1H); 4.06 (M,1H); 4.24 (M,1H); 6.23 (se,1H); 6.59 (s,2H); 6.85 (dd,2.5 and 8.6Hz,1H); 6.96 (D,2.4Hz,1H); 7.40 (M,6H).

Melting point: 198°C

EXAMPLE 31

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-phenethylpiperidin-1-ylamide fumarate



31

Compound 31a: 1-tert-butyloxycarbonyl-4-trifluoromethylsulfonyloxy-1,2,3,6-tetrahydropyridine

Compound **31a** is prepared according to the procedure described for compound **30a** from the following reagents: 1-*tert*-butoxycarbonylpiperidone (20.0 g, 100.4 mmol); diisopropylamine (8.08 ml, 110 mmol); butyllithium (68.8 ml of a 1.6 M solution in hexane, 110 mmol); N-phenyltrifluoromethanesulfonimide (38.2 g, 107 mmol); tetrahydrofuran (300 ml). The crude reaction product is purified by rapid chromatography on a neutral alumina column with a (90/10) petroleum ether/ethyl acetate mixture.

Mass obtained: 19.7 g (51%)

1H NMR (CDCl3): 1.46 (s,9H); 2.43 (M,2H); 3.62 (t,5.7Hz,2H); 4.05 (m,2H); 5.75 (M,1H).

Compound 31b: 1-tert-butyloxycarbonyl-4-phenylethynyl-1,2,3,6-tetrahydropyridine

Compound **31b** is prepared according to the procedure described for compound **30b** from the following reagents: compound **31a** (4 g, 10.3 mmol); phenylacetylene (1.73 ml, 15.7 mmol); triethylamine (5.0 ml, 36.1 mmol); dichloro-*bis*-triphenylphosphinepalladium (170 mg); dimethylformamide (40 ml). The crude product obtained is purified by flash chromatography with a (95/5) petroleum ether/ethyl acetate mixture.

Mass obtained: 2.18 g (yield: 75%)

1H NMR (CDCl3): 1.45 (s,9H); 2.32 (M,2H); 2.52 (t,5.7Hz, 2H); 4.01 (m,2H); 6.08 (M,1H); 7.24-7.32 (m,3H); 7.38-7.43 (m,2H).

Compound 31c: **1-tert-butyloxycarbonyl-4-phenethyl-piperidine**

Compound **31b** (1.09 g, 3.85 mmol) in solution in methanol (50 ml) is hydrogenated (35 PSI) on activated charcoal. After 1 h 30 min, the reaction mixture is filtered, concentrated and then purified by flash chromatography a (90/10) petroleum ether/ether acetate mixture.

Mass obtained: 845 mg (yield: 76%)

1H NMR (CDCl3): 1.03-1.26 (m,2H); 1.46 (s,9H); 1.55-1.75 (m,5H); 2.64 (m,4H); 4.07 (M,2H); 7.16-7.37 (m,5H).

Compound 31d: **4-phenethylpiperidine**

Compound **31d** is prepared according to the procedure used for compound **2b** from the following reagents: compound **31c** (830 mg, 2.87 mmol); trifluoroacetic acid (2.8 ml); dichloromethane (15 ml). The crude reaction product is purified by flash chromatography with a (90/10/1) to (0/100/1) dichloromethane/methanol/ammonium hydroxide gradient.

Mass obtained: 340 mg (yield: 62%)

1H NMR (CDCl3): 1.12-1.44 (m,4H); 1.55 (m,2H); 1.75 (de,2H); 2.53-2.66 (m,4H); 3.10 (de,2H); 7.15-7.31 (m,5H).

Compound 31:

Compound **31** is prepared according to the procedure described for compound **1** from the following reagents: 4-methoxy-3-(4-methylpiperazin-1-yl)aniline (515 mg, 2.33 mmol); compound **31d** (440 mg, 2.33 mmol); triphosgene (230 mg, 0.77 mmol); pyridine (180 ml×2, 2.33 mmol×2); dichloromethane (50 ml). The crude reaction product is purified by flash chromatography with a (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 520 mg (yield: 51%)

This compound is dissolved in methanol and treated with fumaric acid to give the corresponding fumarate. The latter is crystallized from ether.

Elemental analysis for: $C_{26}H_{36}N_4O_2$-1.1$C_4H_4O_4$-0.15H_2O
Calculated values: C 64.40; H 7.24; N 9.88; *Experimental values*: C 64.16; H 7.21; N 10.02

Mass (DCI/NH3): 437 (MH+),294,248,190

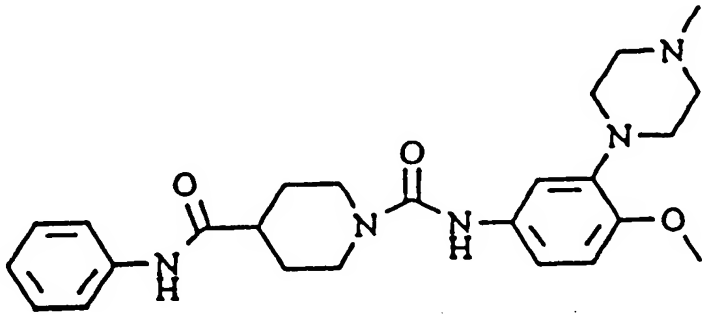
IR (KBr): 3408,3026,2925,2844,1716,1649,1508,1232

1H NMR (DMSO): 1.06 (M,2H); 1.45-1.55 (M,3H); 1.68 (de,2H); 2.30 (s,3H); 2.59 (M,6H), 2.66 (m,2H), 2.94 (M,4H); 3.69 (s,3H); 4.04 (de,2H); 6.55 (s,2.2H); 6.75 (d,8.5Hz,1H); 7.00-7.29 (m,7H); 8.18 (s,1H).

Melting point: 120°C

EXAMPLE 32

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-(N-phenylcarbamoyl)piperidin-1-ylamide fumarate



32

Compound 32a: 1-tert-butyloxycarbonyl-4-(phenylcarbamoyl)-piperidine

Compound **32a** is prepared according to the procedure used for compound **2a** from the following reagents: aniline

(2 ml, 21.8 mmol); 1-*tert*-butyloxycarbonylpiperidine-4-carboxylic acid (5 g, 21.8 mmol); triethylamine (3.1 ml, 21.8 mmol); 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.2 g, 21.8 mmol); 4-dimethylaminopyridine (a spatula tip); dichloromethane (100 ml). The crude reaction product is purified by flash chromatography with a (95/5/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 6.05 g (yield: 91%)

1H NMR (CDCl3): 1.44 (s,9H); 1.61-1.90 (m,4H); 2.36 (m,1H); 2.76 (m,2H); 4.13 (M,1H); 4.19 (M,1H); 7.09 (t,7.3Hz,1H); 7.30 (t,7.5Hz,2H); 7.48 (d,7.9Hz,2H).

<u>Compound 32b:</u> **4-(phenylcarbamoyl)piperidine**

Compound **32b** is prepared according to the procedure used for compound **2b** from the following reagents: compound **32a** (6.05 g, 19.9 mmol); trifluoroacetic acid (20 ml); dichloromethane (100 ml). The crude reaction product is directly used in the next stage.

Mass obtained: 3.5 g (yield: 85%)

1H NMR (CDCl3): 1.61-1.93 (m,5H); 2.37 (tt,3.9 and 11.5Hz,1H); 2.66 (td,3.9 and 11.5Hz,2H); 3.19 (m,2H); 7.09 (t,7.4Hz,1H); 7.31 (m,2H); 7.51 (d,7.9Hz,2H).

<u>Compound 32</u>:

Compound **32** is prepared according to the procedure described for compound **1** from the following reagents: ~~4-methoxy-3-(4-methylpiperizin-1-yl)aniline~~ (2.67 g, 12.1 mmol); compound **32b** (2.47 g, 12.1 mmol); triphosgene (1.2 g, 4.05 mmol); pyridine (935 ml×2, 12.1 mmol×2); dichloromethane (135 ml). The crude reaction product is purified by flash chromatography with a (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 2.97 g (yield: 55%)

This compound is dissolved in methanol and treated with fumaric acid to give the corresponding fumarate. The latter is crystallized from ether.

Elemental analysis for: $C_{25}H_{33}N_5O_3-C_4H_4O_4-0.2H_2O$
Calculated values: C 60.98; H 6.60; N 12.26;
Experimental values: C 61.00; H 6.69; N 12.28

Mass (DCI/NH3): 452 (MH+),248,205

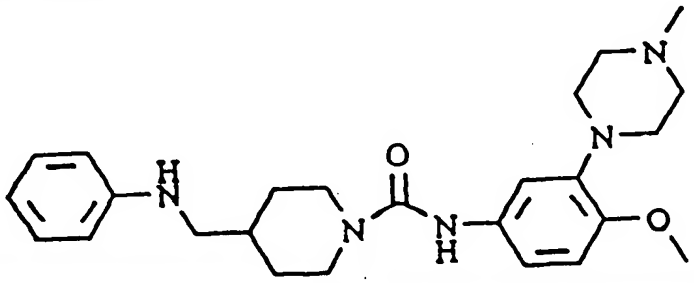
IR (KBr): 3395,2945,2838,1635,1602,1508,1232

1H NMR (DMSO): 1.55 (M,2H); 1.78 (M,2H); 2.32 (s,3H); 2.62 (M,5H); 2.78 (te,2H); 2.96 (M,4H); 3.70 (s,3H); 4.14 (de,2H), 6.56 (s,2H); 6.77 (d,8.7Hz,1H); 6.96-7.08 (M,3H); 7.26 (t,7.8Hz,2H); 7.58 (d,7.7Hz,2H); 8.27 (s,1H); 9.91 (s,1H)..

Melting point: 135°C (amorphous)

EXAMPLE 33

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-(phenylaminomethyl)piperidin-1-ylamide fumarate



33

Compound **33** is prepared according to the same procedure as that described for compound **3a** from the following reagents: compound **32** (500 mg, 1.1 mmol); lithium aluminum hydride (1.8 ml of a 1 M solution in tetrahydrofuran, 1.8 mmol); tetrahydrofuran (10 ml). The crude

product is purified by flash chromatography with a (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 120 mg (yield: 25%)

This compound is dissolved in methanol and treated with fumaric acid to give the corresponding fumarate. The latter is crystallized from ether.

Elemental analysis for: $C_{25}H_{35}N_5O_2$-1.2$C_4H_4O_4$-0.3H_2O
Calculated values: C 61.47; H 6.99; N 12.03; *Experimental values*: C 61.34; H 7.06 N 12.00

Mass (DCI/NH_3): 438 (MH+),248,191

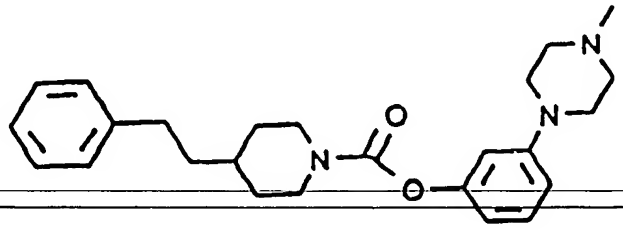
IR (KBr): 3435,2925,2844,1642,1602,1508

1H NMR (DMSO): 1.22 (M,2H); 1.75 (M,3H); 2.33 (s,3H); 2.63 (m,4H), 2.72 (te,2H); 2.92 (M,6H); 3.72 (s,3H); 4.08 (se,1H); 4.18 (se,1H); 6.44-6.54 (m,3H); 6.58 (s,2.4H); 6.78 (D,8.66Hz,1H); 7.01-7.09 (m,4H); 8.22 (s,1H).

Melting point: 105°C

EXAMPLE 34

3-(4-Methylpiperazin-1-yl)phenyl 4-phenylethylpiperidin-1-yloate fumarate



34

Compound **30** (540 mg, 1.24 mmol) is hydrogenated (31 PSI) on Lindlar palladium (130 mg) in solution in ethanol (25 ml) and in the presence of quinoline (520 ml). After

24 h, the reaction mixture is filtered on celite and then purified by flash chromatography with (95/5/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 310 mg (yield: 61%)

This compound is dissolved in methanol and treated with fumaric acid to give the corresponding fumarate. The latter is crystallized from ether.

Elemental analysis for: $C_{25}H_{33}N_3O_2$-1.2$C_4H_4O_4$-0.1H_2O
Calculated values: C 64.24; H 6.18; N 7.66;
Experimental values: C 65.25; H 7.06; N 7.97

Mass (DCI/NH_3): 408(MH+),251

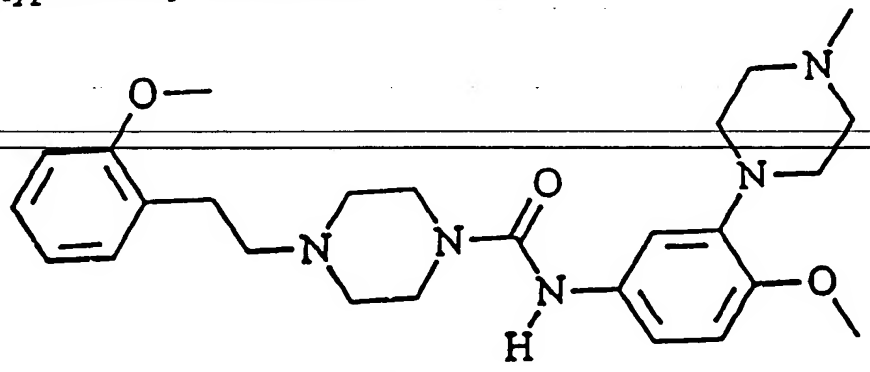
IR (KBr): 3415,2931,2844,2354,1702,1601,1185

1H NMR (DMSO): 1.10 (M,2H); 1.55 (M,3H); 1.77 (M,2H); 2.30 (s,3H); 2.53 (M,6H); 2.88 (M,2H); 3.17 (M,4H); 4.05 (m,2H); 6.50 (dd,1.7 and 7.8Hz,1H); 6.60 (s,2.4H); 6.64 (m,1H); 6.80 (dd,2.1 and 8.1Hz,1H); 7.23 (M,6H).

Melting point: 125°C

EXAMPLE 35

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-(2-methoxyphenethyl)piperazin-1-ylamide fumarate



Compound 35a: 1-(2-methoxybenzylcarbonyl)-4-(*tert*-butyloxycarbonyl)piperazine

Compound **35a** is prepared according to the same procedure as that described for compound **2a** from the following reagents: (2-methoxyphenyl)acetic acid (3.0 g, 18.05 mmol); 1-*tert*-butyloxycarbonylpiperazine (3.36 g, 18.05 mmol); 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.46 g, 18.05 mmol); triethylamine (1.32 ml, 18.05 mmol); 4-dimethylaminopyridine (a spatula tip); dichloromethane (60 ml). The crude reaction product is purified by flash chromatography with a (5/5) ethyl acetate/petroleum ether mixture.

Mass obtained: 4.78 g (yield: 79%)

1H NMR (CDCl,): 1.43 (s,9H); 3.20-3.41 (M,6H); 3.68 (m,4H); 3.81 (s,3H); 6.82-7.26 (M,4H).

Compound 35b: 1-(2-methoxybenzylcarbonyl)piperazine

Compound **35b** is prepared according to the same procedure as that described for compound **2b** from the following reagents: compound **35a** (2.0 g, 5.08 mmol); trifluoroacecic acid (5 ml); dichloromethane (30 ml). The crude product is purified by flash chromatography with a (95/5/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 1.46 g (yield: 98%)

1H NMR (CDCl,): 2.67-2.82 (M,4H); 3.44 (t,4.9Hz,2H); 3.63 (t,4.9Hz,2H); 3.68 (s,2H); 3.82 (s,3H); 6.83-7.26 (M,4H).

Compound 35c: 1-(2-methoxyphenethyl)piperazine

Compound **35c** is prepared according to the same procedure as that described for compound **3a** from the following reagents: compound **35b** (1.40 g, 5.98 mmol); lithium

aluminum hydride (9 ml of a 1 M solution in tetrahydrofuran, 9 mmol); tetrahydrofuran (20 ml). The crude product is purified by flash chromatography with a (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 0.67 g (yield: 51%)

1H NMR ($CDCl_3$): 1.89 (se,1H); 2.53 (m,6H), 2.83 (m,2H); 2.93 (m,4H); 3.82 (s,3H); 6.83-7.26 (M,4H).

Compound 35: Compound **35** is prepared according to the procedure described for compound **1** from the following reagents: triphosgene (225 mg, 0.76 mmol); 4-methoxy-3-(4-methylpiperazin-1-yl)aniline (500 mg, 2.26 mmol); pyridine (180 µl×2, 2.26 mmol×2); 1-(2-methoxyphenethyl)-piperazine (**35c**) (497 mg, 2.26 mmol); dichloromethane (50 ml).

The crude product is purified by flash chromatography with a (90/9/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 0.23 g (yield: 22%)

This compound is dissolved in methanol and treated with fumaric acid to give the corresponding fumarate. The latter is crystallized from ether.

Elemental analysis for: $C_{25}H_{37}N_5O_3 \cdot C_4H_4O_4 \cdot 1.6H_2O$

Calculated values: C 58.83; H 7.27; N 11.43; *Experimental values*: C 59.15; H 7.22; N 11.07

Mass (DCI/NH_3): 468 (MH+),248,222

IR (KBr): 3420,2926,1607,1542,1242

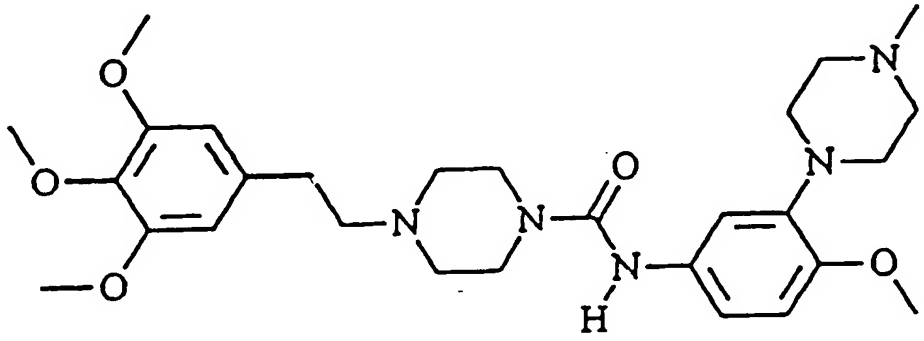
1H NMR (DMSO): 2.17 (s,3H); 2.26 (M,4H); 2.30 (M,4H);

2.54 (M,4H); 2.79 (M,4H); 3.22 (M,4H); 3.52 (s,3H); 3.58 (s,3H); 6.38 (s,2H); 6.60 (d,8.8Hz,1H); 6.66 (t,7.3Hz, 1H); 6.74 (d,7.9Hz,1H); 6.83-6.89 (m,2H); 6.95-7.06 (m,2H); 8.09 (s,1H).

Melting point: 115°C

EXAMPLE 36

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-(3,4,5-trimethoxyphenethyl)piperazin-1-ylamide fumarate



36

Compound 36a: 1-(3,4,5-trimethoxybenzylcarbonyl)-4-(tert-butyloxycarbonyl)piperazine

Compound **36a** is prepared according to the same procedure as that described for compound **2a** from the following reagents: (3,4,5-trimethoxyphenyl)acetic acid (2.0 g, 8.88 mmol); 1-*tert*-butyloxycarbonylpiperazine (1.65 g, 8.88 mmol); 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.70 g, 8.88 mmol); triethylamine (0.65 ml, 8.88 mmol); 4-dimethylaminopyridine (a spatula tip); dichloromethane (60 ml). The crude reaction product is purified by flash chromatography with a (5/5) ethyl acetate/petroleum ether mixture.

Mass obtained: 3.44 g (yield: 99%)

1H NMR (CDCl3): 1.45 (s,9H); 3.27-3.42 (M,6H); 3.59-3.68 (M,4H); 3.84 (M,9H); 6.45 (s,2H).

Compound 36b: **1-(3,4,5-trimethoxybenzylcarbonyl)-piperazine**

Compound **36b** is prepared according to the same procedure as that described for compound **2b** from the following reagents: compound **36a** (3.40 g, 8.63 mmol); trifluoroacetic acid (9 ml); dichloromethane (50 ml). The crude product is purified by flash chromatography with a (95/5/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 2.31 g (yield: 91%)

1H NMR ($CDCl_3$): 2.33-2.45 (m,1H); 2.80-2.94 (M,3H); 3.42-3.72 (M,8H); 3.83 (m,9H); 6.45 (s,2H).

Compound 36c: **1-(3,4,5-trimethoxyphenethyl)piperazine**

Compound **36c** is prepared according to the same procedure as that described for compound **3a** from the following reagents: compound **36b** (2.30 g, 7.82 mmol); lithium aluminum hydride (12 ml of a 1 M solution in tetrahydrofuran, 12 mmol); tetrahydrofuran (30 ml). The crude product is purified by flash chromatography with a (92/8/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 0.98 g (yield: 45%)

1H NMR ($CDCl_3$): 2.49-2.58 (M,6H); 2.68-2.74 (M,2H); 2.89-2.94 (M,4H); 3.83 (m,9H); 6.35 (s,2H).

Compound 36d: **4-methoxy-3-(4-methylpiperazin-1-yl)-1-(*tert*-butyloxycarbonyl)aniline**

A solution of 4-methoxy-3-(4-methylpiperazin-1-yl)aniline which may be prepared according to the method described in European patent 0533266-11 (5.0 g, 22.62 mmol) and di-tert-butyl dicarbonate (5.42 g, 24.88 mmol) in toluene

(100 ml) is heated for 3 h under reflux, under a nitrogen atmosphere. The reaction mixture is then brought to room temperature overnight. The latter is concentrated under reduced pressure, diluted with water and then extracted three times with dichloromethane. The organic phases are pooled, washed once with a saturated sodium chloride solution, dried over magnesium sulfate and concentrated. The crude product is purified by flash chromatography with a (92/8/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 6.39 g (yield: 88%)

1H NMR ($CDCl_3$): 1.46 (s,9H); 2.35 (s,3H); 2.61 (se,4H); 3.09 (se,4H); 3.83 (s,3H); 6.41 (se,1H); 6.75 (d,8.6Hz, 1H); 6.95 (m,2H).

Compound 36: A solution of butyllithium (2.2 ml of a 1.6 M solution in hexane, 3.43 mmol) is slowly added to a suspension of compound **36c** (0.80 g, 2.86 mmol) in tetrahydrofuran (10 ml). During this operation, the reaction mixture is cooled with an ice bath. After 10 min, the latter is delivered by a cannula-type tube over a solution of compound **36d** (0.91 g, 2.86 mmol) in tetrahydrofuran (10 ml) at room temperature. The reaction mixture is then heated under reflux for 4 h and left at room temperature overnight. The mixture is diluted with water and then extracted three times with ethyl acetate. The organic phases are pooled, washed once with a saturated sodium chloride solution, dried over magnesium sulfate and concentrated. The crude product is purified by flash chromatography with a (92/8/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 1.03 g (yield: 69%)

This compound is dissolved in methanol and treated with fumaric acid to give the corresponding fumarate. The latter is crystallized from ether.

Elemental analysis for: $C_{28}H_{41}N_5O_5-C_4H_4O_4-0.2H_2O$

Calculated values: C 59.71; H 7.05; N 10.88;
Experimental values: C 59.38; H 7.20; N 10.77

Mass (DCI/NH_3): 528 (MH+),281,248

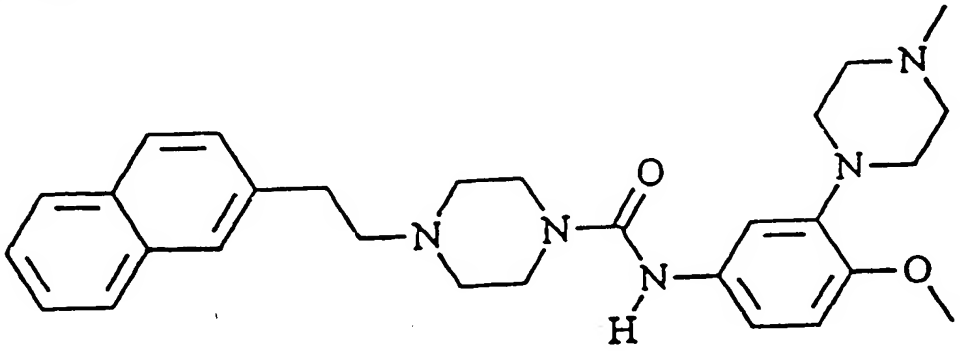
IR (KBr): 3409,2936,2824,1581,1508,1232

1H NMR (DMSO): 2.33 (s,3H); 2.47 (m,4H); 2.56-2.69 (M,8H); 2.97 (se,4H); 3.39 (se,4H); 3.62 (s,3H); 3.73 (s,3H); 3.76 (se,6H); 6.55 (s,2H); 6.57 (s,2H); 6.80 (d,8.8Hz,1H); 7.03 (se,1H); 7.07 (d,8.7Hz,1H); 8.28 (s,1H).

Melting point: 119°C

EXAMPLE 37

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-(2-naphthalen-2-ylethyl)piperazin-1-ylamide fumarate



37

Compound 37a: 1-(naphthalen-2-ylacetyl)-4-(tert-butyloxycarbonyl)piperazine

Compound **37a** is prepared according to the same procedure as that described for compound **2a** from the following reagents: 2-naphthylacetic acid (1.0 g, 5.37 mmol); 1-tert-butyloxycarbonylpiperazine (1.0 g, 5.37 mmol);

1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.03 g, 5.37 mmol); triethylamine (0.39 ml, 5.37 mmol); 4-dimethylaminopyridine (a spatula tip); dichloromethane (50 ml). The crude reaction product is purified by flash chromatography with a (5/5/0.1) ethyl acetate/petroleum ether/ammonium hydroxide mixture.

Mass obtained: 1.63 g (yield: 86%)

1H NMR (CDCl$_3$): 1.40 (s,9H); 3.16 (m,2H); 3.56 (M,4H); 3.60 (m,2H); 3.89 (s,2H); 7.23-7.81 (M,7H).

Compound 37b: **2-naphthalen-2-ylpiperazin-1-ylethanone**

Compound **37b** is prepared according to the same procedure as that described for compound **2b** from the following reagents: compound **37a** (1.63 g, 4.60 mmol); trifluoroacetic acid (5 ml); dichloromethane (20 ml). The crude product is purified by flash chromatography with a (95/5/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 1.15 g (yield: 98%)

1H NMR (CDCl$_3$): 2.63 (t,4.8Hz,2H); 2.83 (t,4.9Hz,2H); 3.45 (t,4.9Hz,2H); 3.65 (t,4.9Hz,2H); 3.90 (s,2H); 7.26-7.51 (M,3H); 7.68 (se,1H); 7.76-7.83 (M,3H).

Compound 37c: **1-(2-naphthalen-2-ylethyl)piperazine**

Compound **37c** is prepared according to the same procedure as that described for compound **3a** from the following reagents: compound **37b** (1.15 g, 4.52 mmol); lithium aluminum hydride (7 ml of a 1 M solution in tetrahydrofuran, 7 mmol); tetrahydrofuran (20 ml). The crude product is purified by flash chromatography with a (90/10/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 0.62 g (yield: 57%)

1H NMR (CDCL$_3$): 1.95 (se,1H); 2.54 (se,4H); 2.68 (m,2H); 2.95 (m,6H); 7.13-7.46 (M,3H); 7.64 (se,1H); 7.75-7.97 (M,3H).

Compound 37: Compound **37** is prepared according to the same procedure as that described for compound **36** from the following reagents: compound **37c** (0.50 g, 2.08 mmol); butyllithium (1.6 ml of a 1.6 M solution in hexane, 2.50 mmol); compound **36d** (0.67 g, 2.08 mmol); tetrahydrofuran (20 ml). The crude product is purified by flash chromatography with a (95/5/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 0.67 g (yield: 66%)

This compound is dissolved in methanol and treated with fumaric acid to give the corresponding fumarate. The latter is crystallized from ether.

Elemental analysis for: $C_{22}H_{37}N_5O_2-C_4H_4O_4-1.5H_2O$

Calculated values: C 65.65; H 6.84; N 11.60;
Experimental values: C 66.36; H 6.92; N 11.55

Mass (DCI/NH$_3$): 488 (MH+),241

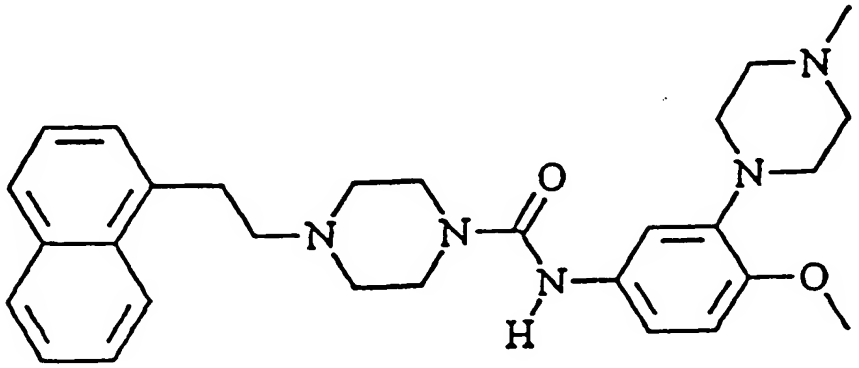
IR (KBr): 3373,1600,1505,1363,1226

1H NMR (DMSO): 2.33 (s,3H); 2.50 (M,4H); 2.66 (M,6H); 2.94 (M,6H); 3.43 (se,4H); 3.72 (s,3H); 6.58 (s,2H); 6.80 (d,8.8Hz,1H); 7.03 (se,1H); 7.07 (d,8.7Hz,1H); 7.42-7.50 (M,3H); 7.74 (s,1H); 7.85 (m,3H); 8.29 (s,1H).

Melting point: 141°C

EXAMPLE 38

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-(2-naphthalen-1-ylethyl)piperazin-1-ylamide fumarate



38

Compound 38a: 1-(naphthalen-1-ylacetyl)-4-(tert-butyloxycarbonyl)piperazine

Compound **38a** is prepared according to the same procedure as that described for compound **2a** from the following reagents: 1-naphthylacetic acid (1.0 g, 5.37 mmol); 1-tert-butyloxycarbonylpiperazine (1.0 g, 5.37 mmol); 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 5.37 mmol); triethylamine (0.39 ml, 5.37 mmol); 4-dimethylaminopyridine (a spatula tip); dichloromethane (50 ml). The crude reaction product is purified by flash chromatography with a (5/5/0.1) ethyl acetate/petroleum ether/ammonium hydroxide mixture.

Mass obtained: 1.58 g (yield: 83%)

1H NMR (CDCl$_3$): 1.44 (s,9H); 3.23 (m,2H); 3.41 (m,4H); 3.67 (m,2H); 4.17 (s,2H); 7.25-7.99 (M,7H).

Compound 38b: 2-naphthalen-1-ylpiperazin-1-ylethanone

Compoun **38b** is prepared according to the same procedure as that described for compound **2b** from the following reagents: compound **38a** (1.58 g, 4.46 mmol); trifluoroacetic acid (4.5 ml); dichloromethane (20 ml). The crude

product is purified by flash chromatography with a (95/5/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 1.09 g (yield: 96%)

1H NMR (CDCl$_3$): 2.68 (t,5.0Hz,2H); 2.86 (t,5.1Hz,2H); 3.41 (t,5.0Hz,2H); 3.68 (t,5.1Hz,2H); 4.15 (s,2H); 7.26-7.58 (M,4H); 7.75-7.99 (M,3H).

Compound 38c: 1-(2-naphthalen-1-ylethyl)piperazine

Compound **38c** is prepared according to the same procedure as that described for compound **3a** from the following reagents: compound **38b** (0.92 g, 3.62 mmol); lithium aluminum hydride (5.5 ml of a 1 M solution in tetrahydrofuran, 5.5 mmol); tetrahydrofuran (20 ml). The crude product is purified by flash chromatography with a (92/8/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 0.22 g (yield: 25%)

1H NMR (CDCl$_3$): 2.52 (se,4H); 2.64 (m,2H); 2.90 (se,4H); 3.21 (m,2H); 7.27-7.46 (M,4H); 7.64 (d,7.9Hz,1H); 7.77 (d,7.8Hz,1H); 8.09 (d,7.8Hz,1H).

Compound 38: Compound **38** is prepared according to the same procedure as that described for compound **36** from the following reagents: compound **38c** (0.21 g, 0.88 mmol); butyllithium (0.7 ml of a 1.6 M solution in hexane, 1.06 mmol); compound **36d** (0.28 g, 0.88 mmol); tetrahydrofuran (20 ml). The crude product is purified by flash chromatography with a (93/7/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 0.29 g (yield: 68%)

This compound is dissolved in methanol and treated with

fumaric acid to give the corresponding fumarate. The latter is crystallized from ether.

Elemental analysis for: $C_{29}H_{37}N_5O_2$-1.1$C_4H_4O_4$-0.5H_2O

Calculated values: C 65.65; H 6.84; N 11.60;
Experimental values: C 65.06; H 7.08; N 11.47

Mass (DCI/NH_3): 488 (MH+),248

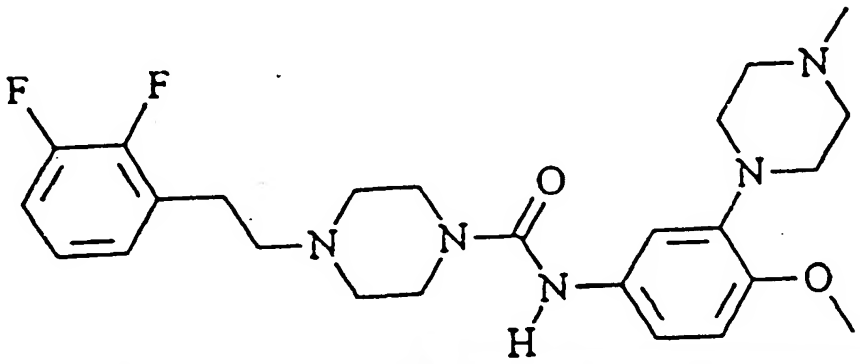
IR (KBr): 3373,1600,1505,1363,1226

1H NMR (DMSO): 2.33 (s,3H); 2.50 (M,10H); 2.97 (se,4H); 3.27 (m,2H); 3.46 (se,4H); 3.73 (s,3H); 6.58 (s,2H); 6.80 (d,8.6Hz,1H); 7.07 (se,1H); 7.09 (d,8.5Hz,1H); 7.42 (se,2H); 7.51-7.58 (M,2H); 7.78 (d,6.3Hz,1H); 7.92 (d,7.8Hz,1H); 8.08 (d,8.2Hz,1H); 8.30 (s,1H).

Melting point: 143°C

EXAMPLE 39

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-(2,3-difluorophenethyl)piperazin-1-ylamide fumarate



Compound 39a: 1-(2,3-difluorobenzylcarbonyl)-4-(tert-butyloxycarbonyl)piperazine

Compound **39a** is prepared according to the same procedure as that described for compound **2a** from the following

reagents: (2,3-difluorophenyl)acetic acid (1.0 g, 5.81 mmol); 1-tert-butyloxycarbonylpiperazine (1.08 g, 5.81 mmol); 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.11 g, 5.81 mmol); triethylamine (0.43 ml, 5.81 mmol); 4-dimethylaminopyridine (a spatula tip); dichloromethane (25 ml). The crude reaction product is purified by flash chromatography with a (5/5/0.1) ethyl acetate/petroleum ether/ammonium hydroxide mixture.

Mass obtained: 1.51 g (yield: 76%)

1H NMR (CDCl$_3$): 1.46 (S,9H); 3.42 (M,6H); 3.61 (m,2H); 3.74 (s,2H); 7.03-7.13 (M,3H).

Compound 39b: 1-(2,3-difluorobenzylcarbonyl)piperazine

Compound **39b** is prepared according to the same procedure as that described for compound **2b** from the following reagents: compound **39a** (1.51 g, 4.44 mmol); trifluoroacetic acid (5 ml); dichloromethane (20 ml). The crude product is purified by flash chromatography with a (90/10/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 0.88 g (yield: 83%)

1H NMR (CDCl$_3$): 1.76 (m,4H); 3.45 (t,5.1Hz,2H); 3.59 (t,5.1Hz,2H); 3.71 (se,2H); 7.00-7.05 (M,3H).

Compound 39c: 1-(2,3-difluorophenethyl)piperazine

Compound **39c** is prepared according to the same procedure as that described for compound **3a** from the following reagents: compound **39b** (0.88 g, 3.66 mmol); lithium aluminum hydride (5.5 ml of a 1 M solution in tetrahydrofuran, 5.5 mmol); tetrahydrofuran (20 ml). The crude product is purified by flash chromatography with a (94/6/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 0.33 g (yield: 40%)

1H NMR ($CDCl_3$): 2.51-2.62 (M,6H); 2.83-2.95 (M,6H); 6.97-7.03 (M,3H).

Compound 39: Compound 39 is prepared according to the same procedure as that described for compound 36 from the following reagents: compound 39c (0.14 g, 0.62 mmol); butyllithium (0.5 ml of a 1.6 M solution in hexane, 0.74 mmol); compound 36d (0.20 g, 0.62 mmol); tetrahydrofuran (10 ml). The crude product is purified by flash chromatography with a (95/5/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 0.11 g (yield: 38%)

This compound is dissolved in methanol and treated with fumaric acid to give the corresponding fumarate. The latter is crystallized from ether.

Elemental analysis for: $C_{25}H_{33}N_5O_2F_2$-$C_4H_4O_4$-$2H_2O$

Calculated values: C 59.07; H 6.32; N 11.88; *Experimental values*: C 57.94; H 6.44; N 11.44

Mass (DCI/NH_3): 474 (MH+),248,227

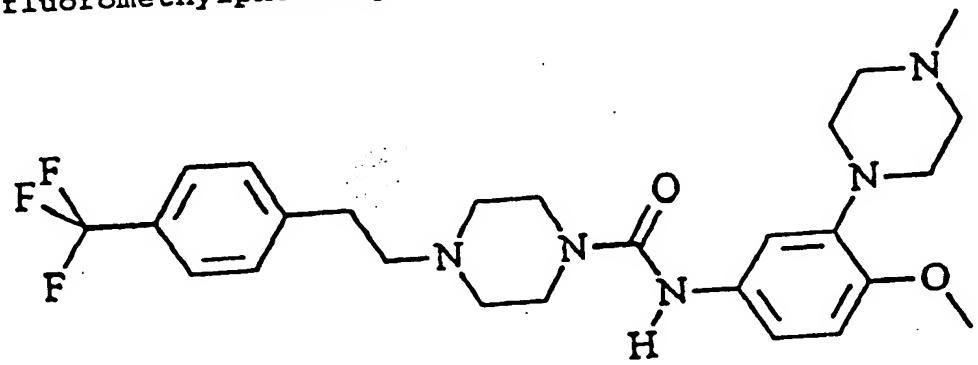
IR (KBr): 3420,2948,1638,1511,1239

1H NMR (DMSO): 2.33 (s,3H); 2.50-2.61 (M,10H); 2.87 (m,2H); 2.97 (se,4H); 3.40 (se,4H); 3.72 (s,3H); 6.58 (s,2H); 6.79 (d,8.7Hz,1H); 7.06-7.29 (M,5H); 8.27 (s,1H).

Melting point: 110°C

EXAMPLE 40

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-(4-trifluoromethylphenethyl)piperazin-1-ylamide fumarate



40

Compound 40a: **1-(4-trifluoromethylbenzylcarbonyl)-4-(*tert*-butyloxycarbonyl)piperazine**

Compound **40a** is prepared according to the same procedure as that described for compound **2a** from the following reagents: (4-trifluoromethylphenyl)acetic acid (1.0 g, 4.90 mmol); 1-*tert*-butyloxycarbonylpiperazine (0.91 g, 4.90 mmol); 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (0.94 g, 4.90 mmol); triethylamine (0.34 ml, 4.90 mmol); 4-dimethylaminopyridine (a spatula tip); dichloromethane (50 ml). The crude reaction product is purified by flash chromatography with a (5/5/0.1) ethyl acetate/petroleum ether/ammonium hydroxide mixture.

Mass obtained: 1.44 g (yield: 79%)
1H NMR ($CDCl_3$): 1.45 (s,9H); 3.30 (m,2H); 3.38 (m,4H); 3.61 (m,2H); 3.79 (s,2H); 7.33-7.60 (M,4H).

Compound 40b: **1-(4-trifluoromethylbenzylcarbonyl)piperazine**

Compound **40b** is prepared according to the same procedure as that described for compound **2b** from the following reagents: compound **40a** (1.44 g, 3.87 mmol); trifluoroacetic acid (4 ml); dichloromethane (20 ml). The crude

product is purified by flash chromatography with a (90/10/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 1.0 g (yield: 95%)

1H NMR (CDCl$_3$): 2.72 (t,4.9Hz,2H); 2.82 (t,5.2Hz,2H); 3.42 (t,4.9Hz,2H); 3.62 (t,5.0Hz,2H); 3.76 (se,2H); 7.33 (m,2H); 7.57 (m,2H).

Compound 40c: **1-(4-trifluoromethylphenethyl)piperazine**

Compound **40c** is prepared according to the same procedure as that described for compound **3a** from the following reagents: compound **40b** (1.0 g, 3.68 mmol); lithium aluminum hydride (5.5 ml of a 1 M solution in tetrahydrofuran, 5.5 mmol); tetrahydrofuran (20 ml). The crude product is purified by flash chromatography with a (94/6/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 0.38 g (yield: 40%)

1H NMR (CDCl$_3$): 1.65 (se,4H); 2.50 (se,4H); 2.59 (m,2H); 2.86 (m,2H); 2.92 (M,4H); 7.31 (m,2H); 7.53 (m,2H).

Compound 40: Compound **40** is prepared according to the same procedure as that described for compound **36** from the following reagents: compound **40c** (0.37 g, 1.43 mmol); butyllithium (1.08 ml of a 1.6 M solution in hexane, 1.72 mmol); compound **36d** (0.46 g, 1.43 mmol); tetrahydrofuran (20 ml). The crude product is purified by flash chromatography with a (92/8/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 0.17 g (yield: 24%)

This compound is dissolved in methanol and treated with fumaric acid to give the corresponding fumarate. The

latter is crystallized from ether.

Elemental analysis for: $C_{26}H_{34}N_5O_2F_3-C_4H_4O_4-1.1H_2O$

Calculated values: C 57.96; H 6.16; N 11.27;
Experimental values: C 57.44; H 6.09; N 11.07

Mass (DCI/NH_3): 506 (MH+), 259, 222

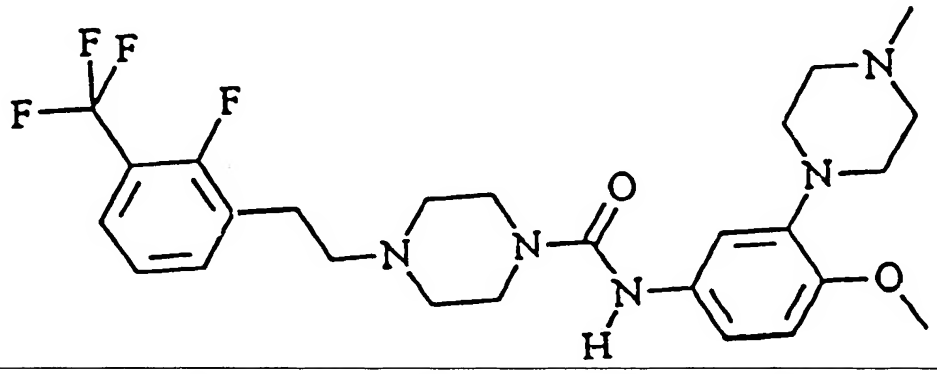
IR (KBr): 3426, 2917, 1619, 1502, 1326

1H NMR (DMSO): 2.33 (s,3H); 2.45 (m,4H); 2.61 (M,6H); 2.86 (t,7.5Hz,2H); 2.97 (se,4H); 3.41 (se,4H); 3.73 (s,3H); 6.58 (s,2H); 6.79 (d,8.7Hz,1H); 7.00 (se,1H); 7.07 (d,8.7Hz,1H); 7.48 (d,7.9Hz,2H); 7.64 (d,7.9Hz,2H); 8.28 (s,1H).

Melting point: 126°C

EXAMPLE 41

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-(2-fluoro-3-trifluoromethylphenethyl)piperazin-1-ylamide fumarate



41

Compound 41a: **1-(2-fluoro-3-trifluoromethylbenzyl-carbonyl)-4-(tert-butyloxycarbonyl)piperazine**

Compound **41a** is prepared according to the same procedure

as that described for compound **2a** from the following reagents: (2-fluoro-3-trifluoromethylphenyl)acetic acid (3.0 g, 13.51 mmol); 1-*tert*-butyloxycarbonylpiperazine (2.52 g, 13.51 mmol); 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (2.59 g, 13.51 mmol); triethylamine (1.80 ml, 13.51 mmol); 4-dimethylaminopyridine (a spatula tip); dichloromethane (60 ml). The crude reaction product is purified by flash chromatography with a (4/6) ethyl acetate/petroleum ether mixture.

Mass obtained: 4.70 g (yield: 89%)

1H NMR ($CDCl_3$): 1.47 (s,9H); 3.43 (M,4H); 3.51 (Mm,2H); 3.62 (m,2H); 3.77 (s,2H); 7.20-7.22 (M,1H); 7.45-7.55 (M,2H).

<u>Compound 41b</u>: **1-(2-fluoro-3-trifluoromethylbenzyl-carbonyl)piperazine**

Compound **41b** is prepared according to the same procedure as that described for compound **2b** from the following reagents: compound **41a** (4.69 g, 12.02 mmol); trifluoroacetic acid (13 ml); dichloromethane (50 ml). The crude product is purified by flash chromatography with a (90/10/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 3.33 g (yield: 96%)

1H NMR ($CDCl_3$): 2.85 (M,4H); 3.52 (t,4.6Hz,2H); 3.64 (m,2H); 3.76 (s,2H); 7.20-7.26 (m,1H); 7.51-7.55 (m,2H).

<u>Compound 41c:</u> **1-(2-fluoro-3-trifluoromethylphenethyl)-piperazine**

Compound **41c** is prepared according to the same procedure as that described for compound **3a** from the following reagents: compound **41b** (2.71 g, 9.36 mmol); lithium aluminum hydride (14 ml of a 1 M solution in ether,

14 mmol); ether (50 ml). The crude product is purified by flash chromatography with a (95/5/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 1.67 g (yield: 65%)

1H NMR (DMSO): 2.34 (M,4H); 2.65 (M,4H); 2.83 (M,2H); 3.06 (m,2H); 7.31-7.35 (m,1H); 7.61-7.81 (m,2H).

Compound 41: Compound **41** is prepared according to the same procedure as that described for compound **36** from the following reagents: compound **41c** (1.16 g, 3.62 mmol); butyllithium (2.7 ml of a 1.6 M solution in hexane, 4.34 mmol); compound **36d** (1.0 g, 3.62 mmol); tetrahydrofuran (20 ml). The crude product is purified by chromatography with a (95/5/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 1.11 g (yield: 59%)

This compound is dissolved in methanol and treated with fumaric acid to give the corresponding fumarate. The latter is crystallized from ether.

Elemental analysis for: $C_{26}H_{33}N_5O_2F_4-C_4H_4O_4-0.29H_2O$

Calculated values: C 56.33; H 5.83; N 10.95;
Experimental values: C 56.42; H 6.00; N 10.76

Mass (DCI/NH$_3$): 524 (MH+),277,248

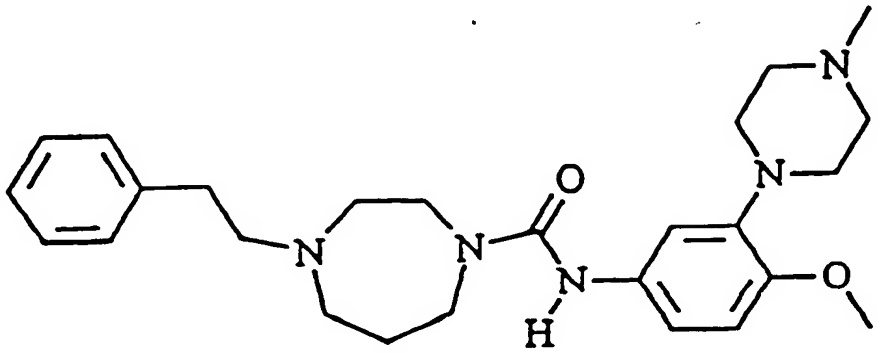
IR (KBr): 3386,2953,2830,1648,1508,1333

1H NMR (DMSO): 2.36 (s, 3H), 2.44 (t,4.40 Hz, 4H), 2.50 (m, 2H), 2.59 (t,7.40, 2H), 2.67 (se, 3H), 2.88 (t,7.4 Hz, 2H), 2.98 (se, 3H), 3.39 (se, 4H), 3.72 (s, 3H), 6.58 (s, 2H), 6.79 (d,8.8 Hz, 1H), 7.02-7.09 (M, 2H), 7.34 (t,7.7 Hz,1H), 7.60 (t,7.2 Hz, 1H), 7.70 (t,7.2 Hz, 1H), 8.28 (s, 1H).

Melting point: 124°C

EXAMPLE 42

N-[4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl]-4-phenethylhomopiperazin-1-ylamide fumarate



42

Compound 42a: 1-benzylcarbonyl-4-(*tert*-butyloxycarbonyl)homopiperazine

Compound **42a** is prepared according to the same procedure as that described for compound **2a** from the following reagents: phenylacetic acid (1.0 g, 7.35 mmol); 1-*tert*-butyloxycarbonylhomopiperazine (1.47 g, 7.35 mmol); 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.41 g, 13.51 mmol); triethylamine (0.54 ml, 7.35 mmol); 4-dimethylaminopyridine (a spatula tip); dichloromethane (60 ml). The crude reaction product is purified by flash chromatography with a (5/5/0.1) ethyl acetate/petroleum ether/ammonium hydroxide mixture.

Mass obtained: 1.79 g (yield: 77%)

1H NMR ($CDCl_3$): 1.45 (s,9H); 1.72 (m,2H); 3.27 (m,3H); 3.47-3.53 (M,4H); 3.65 (se,1H); 3.73 (s,2H); 7.24-7.33 (M,5H).

Compound 42b: 1-benzylcarbonylhomopiperazine

Compound **42b** is prepared according to the same procedure

as that described for compound **2b** from the following reagents: compound **42a** (1.76 g, 5.53 mmol); trifluoroacetic acid (6 ml); dichloromethane (20 ml). The crude product is purified by flash chromatography with a (90/10/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 1.04 g (yield: 87%)

1H NMR (CDCl$_3$): 1.71 (t,6.0Hz,1H); 1.81 (t,6.0Hz,1H); 2.80 (m,3H); 2.95 (t,5.4Hz,1H); 7.22-7.34 (M,5H).

Compound 42c: 1-phenethylhomopiperazine

Compound **42c** is prepared according to the same procedure as that described for compound **3a** from the following reagents: compound **42b** (1.01 g, 2.63 mmol); lithium aluminum hydride (7 ml of a 1 M solution in tetrahydrofuran, 14 mmol); tetrahydrofuran (20 ml). The crude product is purified by flash chromatography with a (90/10/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 0.43 g (yield: 46%)

1H NMR (DMSO): 1.84 (m,2H); 2.66 (se,8H); 2.85 (se,1H); 2.98 (M,4H); 7.07-7.37 (M,5H).

Compound 42: Compound **42** is prepared according to the same procedure as that described for compound **36** from the following reagents: compound **42c** (0.40 g, 1.56 mmol); butyllithium (1.2 ml of a 1.6 M solution in hexane, 1.87 mmol); compound **36d** (0.63 g, 1.56 mmol); tetrahydrofuran (20 ml). The crude product is purified by flash chromatography with a (95/5/1) dichloromethane/methanol/ammonium hydroxide mixture.

Mass obtained: 0.63 g (yield: 90%)

This compound is dissolved in methanol and treated with fumaric acid to give the corresponding fumarate. The latter is crystallized from ether.

Elemental analysis for: $C_{26}H_{37}N_5O_2-C_4H_4O_4-0.6H_2O$

Calculated values: C 63.47; H 7.28; N 12.34;
Experimental values: C 63.63; H 7.50; N 12.34

Mass (DCI/NH_3): 452 (MH+),248,205

IR (KBr): 3408,1645,1497,1355,1230

1H NMR (DMSO): 1.83 (se, 2H), 2.33 (s,3H), 2.63 (se, 4H), 2.75 (se, 6H), 2.79 (se, 2H), 2.98 (se 4H), 3.50 (t,5.9 Hz, 2H), 3.55 (se, 2H), 3.73 (s, 3H), 6.57 (s, 2H), 6.79 (d,8.8 Hz, 1H), 7.06 (se,1H); 7.10 (d,8.8Hz,1H); 7.15-7.28 (M, 5H), 8.00 (s, 1H).

Melting point: 131°C

The derivatives of the present invention are potent $5HT_{1D}$ receptor antagonists as shown by binding studies and studies of antagonism of inhibition of adenylate cyclase (stimulated by forskolin) by a $5HT_{1D}$ agonist such as serotonin, sumatriptan or 5-CT, studies which were carried out on cloned human $5HT_{1D\alpha}$ and $5HT_{1D\beta}$ receptors.

The human $5HT_{1D\alpha}$ and $5HT_{1D\beta}$ receptors were cloned according to the sequences published by M. Hamblin and M. Metcalf, Mol. Pharmacol., **40**, 143 (1991) and Weinshenk et al., Proc. Natl. Acad. Sci. **89**, 3630 (1992).

Transient transfection and permanent transfection of the genes for these receptors was carried out in Cos-7 and CHO-K_1 cell lines using an electroporator.

The HeLa HA7 cell line expressing the human $5HT_{1A}$ receptor was obtained from Tulco (Duke Univ., Durham, N.C., USA)

and cultured according to the method of Fargin et al., J. Biol. Chem. **264**, 14848 (1989).

Study of the binding of the derivatives of the present invention with the human $5HT_{1Dα}$, $5HT_{1Dβ}$ and $5HT_{1A}$ receptors was carried out according to the method described by P. Pauwels and C. Palmier (Neuropharmacology, **33**, 67, 1994).

The incubation media for these binding measurements comprise 0.4 ml of cell membrane preparation, 0.05 ml of a tritiated ligand [[3H]-5CT (final concentration: 2 nM) for the $5HT_{1Dα}$ and $5HT_{1Dβ}$ receptors and [3H]-8OH-DPAT (final concentration: 1 nM) for the $5HT_{1A}$ receptor] and 0.05 ml of the molecule to be tested (final concentrations of 0.1 nM to 1000 nM) or 10 μM (final concentration) of seretonin ($5HT_{1Dα}$ and $5HT_{1Dβ}$) or 1 μM (final concentration) of spiroxatrine ($5HT_{1A}$).

Study of the inhibition of the formation of cyclic AMP (stimulated by forskolin) mediated by the human $5HT_{1Dα}$ and $5HT_{1Dβ}$ receptors was carried out in cells transfected with the receptor according to a technique previously described (P. Pauwels and C. Palmier, Neuropharmacology, **33**, 67, 1994; Cell. Pharmacol. **2**, 183, 1995; Cell. Pharmacol. **2**, 49, 1995; Eur. J. of Pharmacol.. (Mol. Pharm.) **290**, 95, 1995).

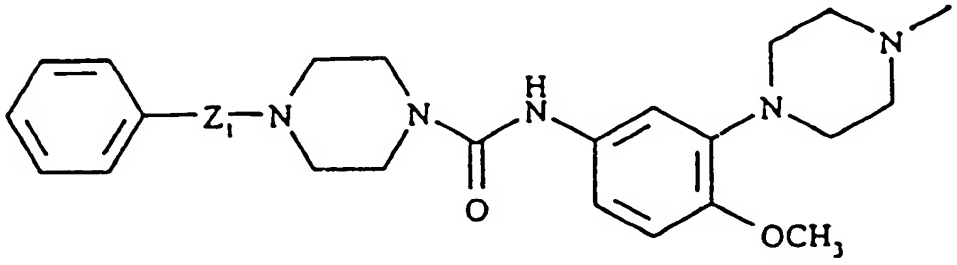
The novel compounds derived from arylpiperazines which are included in the present invention are potent and selective $5HT_{1D}$ receptor antagonists and exhibit the advantage of being particularly selective for the human $5HT_{1D}$ receptors in particular compared with the $5HT_{1A}$, $5HT_{1C}$, $5HT_2$, α_1, α_2 and D_2 receptors.

The derivatives of the present invention are, in addition, capable of inhibiting the contraction induced by 5-hydroxytryptamine in rabbit saphenous vein rings and of antagonizing the inhibition induced by 5-carboxamido-

tryptamin (5CT) at the level of the release of serotonin in guinea-pig brain sections. These two pharmacological models are generally recognized as being particularly relevant in the functional characterization of the $5HT_{1B}$ receptors and, in the case of the products of the present invention, make it possible to demonstrate their antagonistic activity at the level of these receptors.

The derivatives of the present invention are distinguished without ambiguity from the prior art by their novel chemical structure but also by their biological profile. Indeed, comparison of the products of the present invention with the closest prior art (Patent Application FR 9408981) demonstrates unexpectedly the superiority of the products of the present invention as illustrated by the following comparative study (Table 1).

Table 1



	Ki (nM)		
	1Dα	1Dβ	1A
Z_1 is omitted*	340	18	450
Z_1 = CH_2-CH_2**	2.1	1.9	3500

*Compound claimed in patent application FR 9408981

**Compound claimed in the present invention (Example 1)

The comparison described above demonstrates, by way of illustration, that the products of the present invention exhibit the advantage of having a better affinity and a

better selectivity in particular towards the $5HT_{1A}$ receptor, at the level of the $5HT_{1B}$ receptors and in particular at the level of the $5HT_{1D\alpha}$ receptor. These novel and unexpected properties of the $5HT_{1B}$ antagonists claimed in the present invention make them particularly advantageous and useful for the treatment of patients suffering from disorders in the central nervous system. As a result, the present invention also comprises a method for treating such patients, which method uses the administration of an active dose of a compound corresponding to the general formula (I). Studies of antagonistic activity at the level of the cyclase mediated by the $5HT_{1D\alpha}$ and $5HT_{1B}$ receptors demonstrate, moreover, that the illustrative example of the present invention presented in Table 1 above is a potent and silent antagonist, both of the $5HT_{1B}$ but also of the $5HT_{1D\alpha}$ receptor. These properties clearly demonstrate the unique biological characteristics of the derivatives of the present invention, in particular if these data are compared with the data obtained with the derivative GR-127935 which, under the same conditions, appears as an agonist of the human $5HT_{1D\alpha}$ receptor (cf. Pauwels and Colpaert, Neuropharmacol., **34**, 235, 1995).

Moreover, the derivatives of the present invention are also capable of controlling the growth and proliferation of C_6-type glial cells transfected with the gene for the $5HT_{1B}$ receptor and with the gene for $5HT_{1D\alpha}$ receptor, stimulated with a hormonal mediator such as serotonin. By way of example, the examples of the present invention inhibit the incorporation of labeled thymidine (stimulated with 0.1 μM sumatriptan) with an CI_{50} of 10 to 100 nM (method described by P. Pauwels et al., *J. of Neurochemistry*, in press). As such, the derivatives of the present invention therefore also find their usefulness in the treatment of cancers and other disorders linked to cell proliferation.

Pharmaceutical compositions containing, as active ingred-

ients, a compound of general formula (I) or a physiologically acceptable salt of a compound of formula (I) combined with one or more therapeutic agents, such as, for example, antidepressants such as tricyclic antidepressants (for example amitryptyline, clomipramine, desipramine, imipramine), monoamine oxidase inhibitors (for example isocarboxazide, moclobemide, phenelzine or tranylcyclopramine), inhibitors of serotonin reuptake (for example fluvoxamine, sertraline, fluoxetine, paroxetine or citalopram), inhibitors of serotonin and noradrenaline reuptake (for example milnacipran), or α_2 antagonists (for example mianserin, mirtazapine, setiptiline, idazoxan, effaroxan, fluparoxan), should also be considered as being included in the present invention.

The derivatives of the present invention or their physiologically acceptable salts may also be administered in the form of pharmaceutical compositions, in combination with an antagonist of the $5HT_{1A}$ receptor (such as, for example, pindolol, WAY 100135, UH-301 or WAY 100635). This combination is also included in the present invention.

The subject of the present invention is also the pharmaceutical compositions containing, as active ingredient, a compound of general formula I or one of its salts acceptable for pharmaceutical use, mixed or combined with an appropriate excipient. These compositions may take, for example, the form of solid or liquid compositions, of emulsions, lotions or creams.

As solid compositions for oral administration, tablets, pills, powders (gelatin capsules, cachets) or granules may be used. In these compositions, the active ingredient according to the invention is mixed with one or more inert diluents, such as starch, cellulose, sucrose, lactose or silica, under an argon stream. These compositions may also comprise substances other than diluents,

for example one or more lubricants such as magnesium stearate or talc, a coloring, a coating (sugar-coated tablets) or a glaze.

As liquid compositions for oral administration, pharmaceutically acceptable solutions, suspensions, emulsions, syrups and elixirs containing inert diluents such as water, ethanol, glycerol, vegetable oils or paraffin oil may be used. These compositions may comprise substances other than diluents, for example wetting, sweetening, thickening, flavoring or stabilizing products.

Sterile compositions for parenteral administration may be preferably solutions which are aqueous or nonaqueous, suspensions or emulsions. As solvent or vehicle, it is possible to use water, propylene glycol, polyethylene glycol, vegetable oils, in particular olive oil, injectable organic esters, for example ethyl oleate or other suitable organic solvents. These compositions may also contain adjuvants, in particular wetting, isotonizing, emulsifying, dispersing and stabilizing agents. The sterilization may be carried out in several ways, for example by asepticizing filtration, by incorporating sterilizing agents into the composition, by irradiation or by heating. They may also be prepared in the form of sterile solid compositions which may be dissolved at the time of use in sterile water or any other injectable sterile medium.

The compositions for rectal administration are suppositories or rectal capsules which contain, in addition to the active product, excipients such as cocoa butter, semisynthetic glycerides or polyethylene glycols.

Compositions for topical administration may be, for example, creams, lotions, collyria, collutoria, nasal drops or aerosols.

The doses depend on the desired effect, the duration of

treatment and the route of administration used; they are generally between 0.001 g and 1 g (preferably between 0.005 g and 0.25 g) per day, preferably by the oral route for an adult with unit doses ranging from 0.1 mg to 500 mg of active substance, preferably from 1 mg to 50 mg.

In general, the doctor will determine the appropriate dosage according to the age, weight and all the other factors specific to the subject to be treated. The following examples illustrate compositions according to the invention [in these examples, the term "active component" denotes one or more (generally one) of the compounds of formula (I) according to the present invention]:

Tablets

They can be prepared by direct compression or via wet granulation. The direct compression procedure is preferred but it may not be suitable in all cases depending on the doses and the physical properties of the active component.

A - By direction compression

	mg for 1 tablet
active component	10.0
microcrystalline cellulose B.P.C.	89.5
magnesium stearate	0.5
	100.00

The active component is passed through a sieve with a mesh opening of side 250 µm, mixed with the excipients and compressed with the aid of 6.0 mm dies. It is possible to prepare tablets exhibiting other mechanical resistances by modifying the compression weight with the use of appropriate dies.

B - Wet granulation

	mg for one tablet
active component	10.0
lactose Codex	74.5
starch Codex	10.0
pregelatinized corn starch Codex	5.0
magnesium stearate	0.5
Weight at compression	100.0

The active component is passed through a sieve with a mesh opening of 250 µm and mixed with lactose, starch and pregelatinized starch. The mixed powders are moistened with purified water, converted to the granule state, dried, sieved and mixed with magnesium stearate. The lubricated granules are tableted as for the direct compression formulas. A film coating may be applied to the tablets by means of appropriate film-forming materials, for example methyl cellulose or hydroxypropyl methyl cellulose, according to conventional techniques. The tablets may also be coated with sugar.

Capsules

	mg for one capsule
active component	10.0
starch 1500	89.5
magnesium stearate Codex	0.5
Filling weight	100.0

a form of directly compressible starch obtained from the company Colorcon Ltd, Orpington, Kent, Great Britain.

The active component is passed through a sieve with a mesh opening of 250 µm and mixed with the other substances. The mixture is introduced into No. 2 hard gelatin capsules on an appropriate filling machine. It is possible to prepare other dosage units by modifying the filling weight and, when necessary, by changing the size of the capsule.

Syrup

		mg per dose of 5 ml
active component		10.0
sucrose Codex		2750.0
glycerin Codex		500.0
buffer	)	
flavoring	)	
coloring	)	q.s.
preservative	)	
distilled water		5.0

The active component, the buffer, the flavoring, the coloring and the preservative are dissolved in a portion of the water and glycerin is added. The remainder of the water is heated to 80°C and the sucrose is dissolved therein and then cooled. The two solutions are combined, the volume is adjusted and mixed. The syrup obtained is clarified by filtration.

Suppositories

active component		10.0 mg
*Witepsol H15	balance to	1.0 g

* trademark for Adeps Solidus of the European Pharmacopeia

A suspension of the active component is prepared in Witepsol H15 and introduced into an appropriate machine with 1 g suppository molds.

Liquid for administration by the intravenous route

		g/l
active component		2.0
water for injection Codex	balance to	1000.0

Sodium chloride may be added to adjust the tonicity of the solution and to adjust the pH to the maximum stability and/or to facilitate the dissolution of the active component by means of an acid or a dilute alkali or by

adding appropriate buffer salts. The solution is prepared, it is clarified and it is introduced into vials of appropriate size which are sealed by melting the glass. The liquid may also be sterilized for injection by heating in an autoclave according to one of the acceptable cycles. It is also possible to sterilize the solution by filtration and to introduce into a sterile vial under aseptic conditions. The solution may be introduced into the vials under a gaseous atmosphere.

Cartridges for inhalation

	g/cartridge
micronized active component	1.0
lactose Codex	39.0

The active component is micronized in a fluid energy grinder and converted to fine particles before mixing with lactose for tablets in a high-energy mixer. The pulverulent mixture is introduced into No. 3 hard gelatin capsules in an appropriate encapsulating machine. The content of the cartridges is administered with the aid of a powder inhaler.

Pressurized aerosol with metering valve

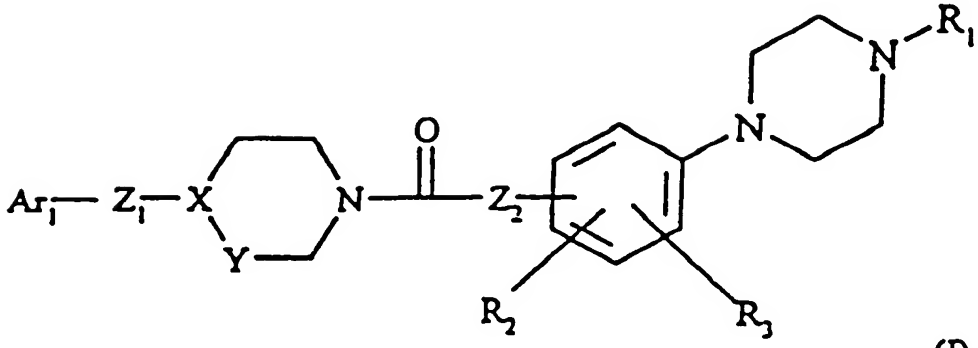
	mg/dose	for 1 can
micronized active component	0.500	120 mg
oleic acid Codex	0.050	12 mg
trichlorofluoromethane for pharmaceutical use	22.25	5.34 g
dichlorodifluoromethane for pharmaceutical use	60.90	14.62 g

The active component is micronized in a fluid energy grinder and converted to fine particles. Oleic acid is mixed with trichlorofluoromethane at a temperature of 10-15°C and the micronized drug is introduced into the solution with the aid of a mixer featuring a high shear-

ing effect. The suspension is introduced in a measured quantity into aluminum aerosol cans on which appropriate metering valves delivering a dose of 85 mg of the suspension are fitted; the dichlorodifluoromethane is introduced into the cans by injection through the valves.

CLAIMS

1. Compounds corresponding to the general formula (I)



(I)

in which:

R_1 represents a hydrogen or a linear or branched alkyl comprising from 1 to 6 carbon atoms,

Z_2 represents O, NH, CH_2O or CH_2NH,

R_2 and R_3, which are identical or different, represent a hydrogen or a group chosen from a linear or branched alkyl, an alkoxy, thioether, nitrile, trifluoromethyl or halogen (F, Cl, Br, I), or, R_2 and R_3, when they are adjacent, taken together, form a 5- or 6-membered ring so as to constitute, for example, a naphthyl, a tetrahydronaphthyl, a benzopyran or a benzodioxane,

X-Y represents NCH_2, $CH-CH_2$, C=CH, N or NCH_2CH_2,

Z_1 represents $-(CH_2)_n-$, $-(CH_2)_n\,CO-$, $-CO-$, $-CO(CH_2)_n-$, $-SO_2-$, $-SO_2(CH_2)_n-$, $-O(CH_2)_n-$, $-O(CH_2)_nCO-$, $-OCO-$, $-NH(CH_2)_n-$, $-NH(CH_2)_nCO-$, $-NHCO-$, $-NHCO(CH_2)_n-$, $-NH(CH_2)_nSO_2-$, $-NHSO_2-$, $-NHSO_2(CH_2)_n-$, $-CH=CHCO-$, $-CCCO-$ $-(CH_2)_nSO_2-$, $-O(CH_2)_nSO_2-$.

In the specific case where X-Y represents $CH-CH_2$, Z_1 may also represent $-O-$,

$-NH-$, $-CONH-$, $-SO_2NH-$, $-OCONH-$, $-NHCOO-$, $NHCONH-$ $-(CH_2)_nNH-$, $-(CH_2)_nO-$, $-CO(CH_2)_nNH-$, $-NH(CH_2)_nO-$, $-NH(CH_2)_nNH-$, $-O(CH_2)_nNH-$, $-O(CH_2)_nO-$, $-CO(CH_2)_nO-$, $-SO_2(CH_2)_nNH-$, $-SO_2(CH_2)_nO-$, $-(CH_2)_nSO_2NH-$, $-(CH_2)_nCONH-$, $-O(CH_2)_nSO_2NH-$, $-O(CH_2)_nCONH-$, $-NH(CH_2)_nSO_2NH-$, $-NH(CH_2)_nCONH-$, $-NHCO(CH_2)_nNH-$, $-NHSO_2(CH_2)_nNH-$ in which n represents an integer between 1 and 6,

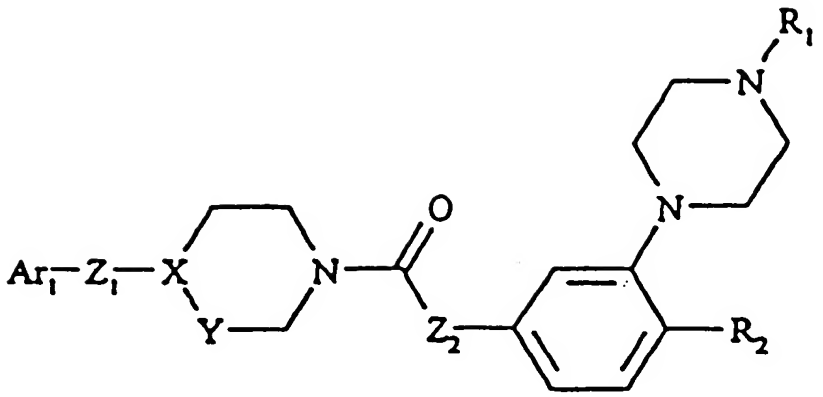
In the specific case where X-Y represents $CH-CH_2$ or C=CH, Z_1 may also represent -CH=CH-, -CC-,

Ar_1 represents an aromatic residue (phenyl, naphthyl or pyridyl) which may be variously substituted, for example, with one or more groups chosen from a linear or branched alkyl comprising from 1 to 6 carbon atoms, a trifluoromethyl, a trifluoromethoxy, a 2,2,2-trifluoroethyl, a phenyl, a benzyl, a cycloalkyl comprising from 3 to 7 carbon atoms, a hydroxyl, a thiol, an alkoxy (OR_4), thioether (SR_4), a nitro (NO_2), a nitrile (CN), an amine (NH_2 or NR_4R_4'), an amine derivative ($NHCOR_4$, $NHSO_2R_4$, $NHCONR_4R_4'$, $NHCO_2R_4$, $NHSO_2NR_4R'_4$), a halogen (fluorine, chlorine, bromine or iodine), a carbonyl (COH, COR_4, $COOR_4$, $CONR_4R'_4$) or a heterocycle which may be optionally substituted such as a 5-membered heterocycle which may contain from 1 to 4 heteroatoms chosen from oxygen, sulfur or nitrogen or with two substituents on adjacent carbons which may form a ring with the aromatic residue to which they are attached, or alternatively the residue $Ar-Z_1$ represents a tetrahydronaphthyl whose bonding with X uses a saturated carbon,

R_4 represents a linear or branched alkyl residue comprising from 1 to 6 carbon atoms, R'_4 represents a hydrogen or a linear or branched alkyl residue comprising from 1 to 6 carbon atoms,

and their salts, hydrates, solvates and bioprecursors which are physiologically acceptable for therapeutic use, the compounds of general formula (I) being provided in the form of geometric and optical isomers and in racemic form.

2. Compounds according to Claim 1, characterized in that they correspond to the general formula Ia:



(Ia)

in which Ar_1, Z_1, X-Y, Z_2 and R_1 are as defined in Claim 1 and R_2 represents a hydrogen, a methyl, a methoxy or a chlorine.

3. Compounds according to Claim 1, characterized in that Z_2 represents O or NH.

4. Compounds according to Claim 1, characterized in that Z_2 represents CH_2O or CH_2NH.

5. Compounds according to Claim 1, characterized in that X-Y represents $N-CH_2$.

6. Compounds according to Claim 1, characterized in that X-Y represents $CH-CH_2$ or C=CH.

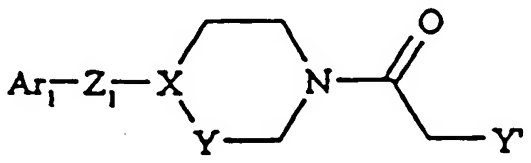
7. Compounds according to Claim 1, characterized in that Z_1 represents $(CH_2)_n$, $CO(CH_2)_n$, $SO_2(CH_2)_n$, $O(CH_2)_n$, $NH(CH_2)_n$ or $NHCO(CH_2)_n$.

8. Compounds according to Claim 1, characterized in that Z_1 represents $(CH_2)_nCO$, CO, $O(CH_2)nCO$, $NH(CH_2)_nCO$ or CH=CHCO.

9. Compounds according to Claim 1, characterized in that Z_1 represents SO_2, $(CH_2)_nSO_2$, $O(CH_2)nSO_2$ or $NH(CH_2)_nSO_2$.

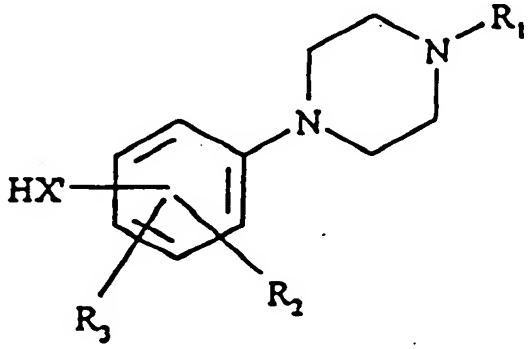
10. Compounds according to Claim 1, characterized in that X-Y represents $CH-CH_2$ and Z_1 represents O, NH, CONH, SO_2NH, OCONH, NHCOO, NHCONH, $(CH_2)_nNH$, $(CH_2)_nO$, $NH(CH_2)_nO$, $O(CH_2)_nNH$ $NH(CH_2)_nNH$, $CO(CH_2)_nNH$ or $CO(CH_2)_nO$.

11. Process for preparing the compounds of formula (I) in which Ar_1, Z_1, X-Y, R_1, R_2 and R_3 are as defined above and Z_2 represents CH_2O or CH_2NH, characterized in that an intermediate of formula (II)



(II)

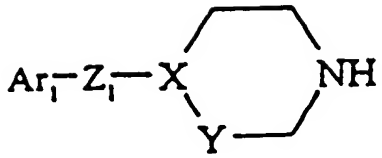
in which Ar_1, Z_1 and X-Y are as defined above and Y' represents a leaving group such as a halogen (chlorine or bromine), a tosylate, a mesylate or a triflate, is condensed with an arylpiperazine of general formula III



(III)

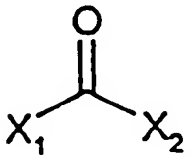
in which X' represents O or NH, and R_1, R_2 or R_3 are as defined above in the presence of an organic or inorganic base.

12. Process for preparing the compounds of formula (I) in which Ar_1, Z_1, X-Y are as defined above and Z_2 represents O or NH, characterized in that an intermediate of formula (III) as defined in Claim 11, and an arylpiperazine of formula (IV)



(IV)

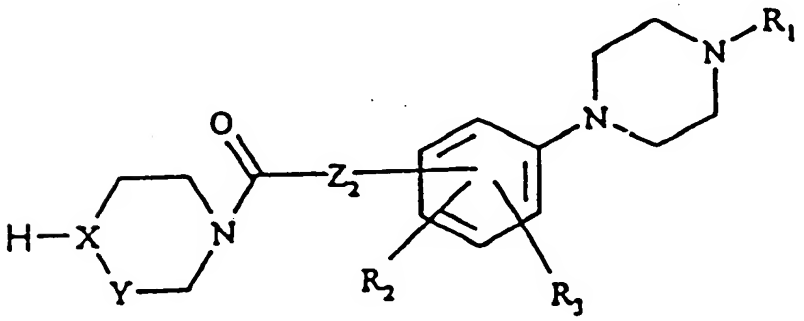
in which Ar_1, Z_1 and X-Y are as defined above, are condensed with an electrophile of formula (XII)



(XII)

in which X_1 and X_2 represent a leaving group such as a halogen (in particular chlorine), an o-alkyl group (in particular the $OCCl_3$ group), a succinimyl, phthalyl or imidiazolyl.

13. Process for preparing the compounds of formula (I) in which X represents a nitrogen, characterized in that an intermediate of formula (XXXI)



(XXXI)

in which R_1, R_2, R_3 and Z_2 are as defined above and X-Y represents N, N-CH_2 or NCH_2CH_2, is condensed with an electrophile of formula (XVII)

$$Ar_1 - Z_1 - L \qquad (XVII)$$

in which Ar_1 and Z_1 are as defined above and L represents a leaving group the choice of which as

well as the choice of the experimental conditions (for carrying out the condensation) will depend on the nature of Z_1.

14. Process for preparing the products of formula (I) in which Ar_1, X-Y, Z_1, Z_2 are as defined above and R_1 represents a hydrogen, characterized in that a compound of formula (I) in which R_1 represents a t-butoxycarbonyl is hydrolyzed in acidic medium.

15. Pharmaceutical compositions containing, as active ingredients, a compound according to one of Claims 1 to 10, in combination with an acceptable pharmaceutical vehicle, as medicaments.

16. Pharmaceutical compositions containing, as active ingredients, a compound according to one of Claims 1 to 10, in combination with an acceptable pharmaceutical vehicle, for both the curative and preventive treatment of depression and of obsessive compulsive disorders or disturbances.

17. Pharmaceutical compositions containing, as active ingredients, a compound according to one of Claims 1 to 10, in combination with an acceptable pharmaceutical vehicle, for both the curative and preventive treatment of anxiety and of panic attacks, of schizophrenia, of aggressiveness, of bulimia, of alcoholism, of pain and of neurodegenerative diseases such as Parkinson's or Alzheimer's diseases.

18. Pharmaceutical compositions containing, as active ingredients, a compound according to one of Claims 1 to 10, in combination with an acceptable pharmaceutical vehicle, for both the curative and preventive treatment of cancers.

19. Pharmaceutical compositions according to one of

Claims 13 to 16, characterized in that they contain, in addition, at least a second combined active ingredient, endowed with antidepressant properties, in particular MILNACIPRAN and/or a 5HT 1A antagonist.

SECTION V

Reference is made to the following documents:

D1: WO-A-9 602 525
D2: EP-A-0 524 146
D3: EP-A-0 606 824
D4: EP-A-0 533 266
D5: EP-A-0 533 267
D6: EP-A-0 533 268
D7: GB-A-2 273 930
D8: WO-A-9 415920
D9: WO-A-9 504 729
D10: WO-A-9 506 044

1). The subject of the present claims is novel in relation to D1, because Z_1 cannot represent a single bond for the claimed derivatives of formula (I).
The subject of the present claims is novel in relation to D2 and D3 because for the derivatives of formula (I) disclosed in these documents, the nitrogen atom attached to R_1 cannot form a piperazinyl ring.
The subject of the present claims is novel in relation to D4-D10 because these documents do not disclose derivatives containing an amide bond with a cyclic amine such as piperazine, piperidine, tetrahydropyridine, pyrrolidine or homopiperazine.

The subject of the present claims is therefore novel in relation to the documents cited in the search report (Article 33(2) PCT).

2). The technical problem underlying the present application could be seen as the provision of new compounds having affinity for the 5-HT_{1B} receptor.

However, the technical problem forming the basis of an application can only be taken into account for discussing an inventive step if it is effectively solved by the subject claimed.

However, at this stage of the examination procedure, it is not credible that practically the entire subject of the claims is a solution to this technical problem. It is known in pharmacochemistry, in particular in the field of receptors, that certain, even minor, structural modifications in a molecule result in a radical modification of the effect.
Consequently, it is not credible on the basis of a single test (see page 107 of the present application) that practically all the compounds of claims of a very wide scope, including moreover expressions which are not limited in their scope, such as "arcmatic residue" "which may be variously substituted", are solutions to the technical problem as defined above.
Even with a Claim 1 limited to a meaning of "aryl" restricted to phenyl, naphthyl or pyridyl which may be optionally substituted with substituents given by way of illustration in Claim 1, it could not be made credible that practically the entire subject claimed is effectively a solution to this technical problem.
It is truly not evident from the data of the present application as well as from the documents cited D1, D4-D10 disclosing 5-HT1D antagonists, which would be the claimed compounds not being of formula (Ia) which are solutions to the technical problem.
The technical problem is therefore to be formulated more broadly, for example the provision of products not necessarily having a pharmacological activity.
The examiner is satisfied that practically the entire subject of the present claims is a solution to this technical problem.
However, there is no technical prejudice to the synthesis of the claimed compounds which may be prepared by conventional methods.
The subject of the present claims therefore lacks an inventive step (Article 33(3) PCT).

SECTION VIII

The expression "biological precursor" is not clear in its scope (Article 6 PCT).

A reference to the claims of products should be introduced into the claims of process 12-14.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/FR 97/00203

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D295/20 C07D295/22 C07D211/32 C07D211/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 02525 A (PIERRE FABRE MEDICAMENT) 1 February 1996 see the whole document ---	1-19
A	EP 0 524 146 A (CIBA-GEIGY AG) 20 January 1993 see page 25 - page 29; claims ---	1-19
A	EP 0 606 824 A (CIBA-GEIGY AG) 20 July 1994 see page 21 - page 26; claims ---	1-19
A	EP 0 533 266 A (GLAXO GROUP LIMITED) 24 March 1993 cited in the application see page 36 - page 42; claims ---	1-19

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 May 1997	21.05 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Luyten, H

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/FR 97/00203

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 533 267 A (GLAXO GROUP LIMITED) 24 March 1993 cited in the application see page 31 - page 35; claims	1-19
A	EP 0 533 268 A (GLAXO GROUP LIMITED) 24 March 1993 cited in the application see page 33 - page 38; claims	1-19
A	GB 2 273 930 A (GLAXO GROUP LIMITED) 6 July 1994 cited in the application see page 43 - page 47; claims	1-19
A	WO 94 15920 A (GLAXO GROUP LIMITED) 21 July 1994 cited in the application see page 37 - page 44; claims	1-19
A	WO 95 04729 A (SMITH KLINE BEECHAM) 16 February 1995 cited in the application see page 25 - page 28; claims	1-19
A	WO 95 06044 A (SMITH KLINE BEECHAM) 2 March 1995 see page 16 - page 20; claims	1-19

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter mal Application No
PCT/FR 97/00203

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INTERNATIONAL SEARCH REPORT

information on patent family members

Inter nal Application No
PCT/FR 97/00203

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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WO 9506044 A	02-03-95	EP 0714389 A	05-06-96

RAPPORT DE RECHERCHE INTERNATIONALE

Dem Internationale No
PCT/FR 97/00203

A. CLASSEMENT DE L'OBJET DE LA DEMANDE
CIB 6 C07D295/20 C07D295/22 C07D211/32 C07D211/16

Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB

B. DOMAINES SUR LESQUELS LA RECHERCHE A PORTE

Documentation minimale consultee (systeme de classification suivi des symboles de classement)
CIB 6 C07D

Documentation consultee autre que la documentation minimale dans la mesure où ces documents relevent des domaines sur lesquels a porte la recherche

Base de donnees électronique consultée au cours de la recherche internationale (nom de la base de données, et si cela est realisable, termes de recherche utilisés)

C. DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie *	Identification des documents cités, avec, le cas échéant, l'indication des passages pertinents	no. des revendications visées
A	WO 96 02525 A (PIERRE FABRE MEDICAMENT) 1 Février 1996 voir le document en entier ---	1-19
A	EP 0 524 146 A (CIBA-GEIGY AG) 20 Janvier 1993 voir page 25 - page 29; revendications ---	1-19
A	EP 0 606 824 A (CIBA-GEIGY AG) 20 Juillet 1994 voir page 21 - page 26; revendications ---	1-19
A	EP 0 533 266 A (GLAXO GROUP LIMITED) 24 Mars 1993 cité dans la demande voir page 36 - page 42; revendications --- -/--	1-19

[X] Voir la suite du cadre C pour la fin de la liste des documents

[X] Les documents de familles de brevets sont indiqués en annexe

* Categories spéciales de documents cités:

"A" document définissant l'état général de la technique, non considéré comme particulièrement pertinent

"E" document antérieur, mais publié à la date de dépôt international ou après cette date

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"T" document ultérieur publié après la date de dépôt international ou date de priorité et n'appartenant pas à l'état de la technique pertinent, mais cité pour comprendre le principe ou la théorie constituant la base de l'invention

"X" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme nouvelle ou comme impliquant une activité inventive par rapport au document considéré isolément

"Y" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme impliquant une activité inventive lorsque le document est associé à un ou plusieurs autres documents de même nature, cette combinaison étant évidente pour une personne du métier

"&" document qui fait partie de la même famille de brevets

Date à laquelle la recherche internationale a été effectivement achevée	Date d'expédition du present rapport de recherche internationale
12 Mai 1997	21.05.97

Nom et adresse postale de l'administration chargée de la recherche internationale	Fonctionnaire autorisé
Office Européen des Brevets, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tél. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Luyten, H

1

RAPPORT DE RECHERCHE INTERNATIONALE

Dem Internationale No
PCT/FR 97/00203

C.(suite) DOCUMENTS CONSIDERES COMME PERTINENTS

Categorie *	Identification des documents cites, avec, le cas echeant, l'indication des passages pertinents	no. des revendications visees
A	EP 0 533 267 A (GLAXO GROUP LIMITED) 24 Mars 1993 cité dans la demande voir page 31 - page 35; revendications ---	1-19
A	EP 0 533 268 A (GLAXO GROUP LIMITED) 24 Mars 1993 cité dans la demande voir page 33 - page 38; revendications ---	1-19
A	GB 2 273 930 A (GLAXO GROUP LIMITED) 6 Juillet 1994 cité dans la demande voir page 43 - page 47; revendications ---	1-19
A	WO 94 15920 A (GLAXO GROUP LIMITED) 21 Juillet 1994 cité dans la demande voir page 37 - page 44; revendications ---	1-19
A	WO 95 04729 A (SMITH KLINE BEECHAM) 16 Février 1995 cité dans la demande voir page 25 - page 28; revendications ---	1-19
A	WO 95 06044 A (SMITH KLINE BEECHAM) 2 Mars 1995 voir page 16 - page 20; revendications -----	1-19

RAPPORT DE RECHERCHE INTERNATIONALE

*Renseignements relatifs aux membres de familles de brevets

Demande internationale No
PCT/FR 97/00203

Document brevet cité au rapport de recherche	Date de publication	Membre(s) de la famille de brevet(s)	Date de publication
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RAPPORT DE RECHERCHE INTERNATIONALE

*Renseignements relatifs aux membres de familles de brevets

Dem Internationale No
PCT/FR 97/00203

Document brevet cité au rapport de recherche	Date de publication	Membre(s) de la famille de brevet(s)	Date de publication
EP 533267 A		ZA 9207106 A	17-03-94
EP 533268 A	24-03-93	AP 303 A	28-01-94
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		JP 9501171 T	04-02-97
WO 9506044 A	02-03-95	EP 0714389 A	05-06-96

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/FR 97/00203

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D295/20 C07D295/22 C07D211/32 C07D211/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 02525 A (PIERRE FABRE MEDICAMENT) 1 February 1996 see the whole document ---	1-19
A	EP 0 524 146 A (CIBA-GEIGY AG) 20 January 1993 see page 25 - page 29; claims ---	1-19
A	EP 0 606 824 A (CIBA-GEIGY AG) 20 July 1994 see page 21 - page 26; claims ---	1-19
A	EP 0 533 266 A (GLAXO GROUP LIMITED) 24 March 1993 cited in the application see page 36 - page 42; claims ---	1-19

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
12 May 1997	21.05 97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	**Authorized officer** Luyten, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Applicaton No
PCT/FR 97/00203

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 533 267 A (GLAXO GROUP LIMITED) 24 March 1993 cited in the application see page 31 - page 35; claims	1-19
A	EP 0 533 268 A (GLAXO GROUP LIMITED) 24 March 1993 cited in the application see page 33 - page 38; claims	1-19
A	GB 2 273 930 A (GLAXO GROUP LIMITED) 6 July 1994 cited in the application see page 43 - page 47; claims	1-19
A	WO 94 15920 A (GLAXO GROUP LIMITED) 21 July 1994 cited in the application see page 37 - page 44; claims	1-19
A	WO 95 04729 A (SMITH KLINE BEECHAM) 16 February 1995 cited in the application see page 25 - page 28; claims	1-19
A	WO 95 06044 A (SMITH KLINE BEECHAM) 2 March 1995 see page 16 - page 20; claims	1-19

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9602525 A	01-02-96	FR 2722788 A	26-01-96
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EP 533266 A	24-03-93	AU 2452992 A	25-03-93
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		ZA 9207107 A	08-09-93
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		US 5358948 A	25-10-94

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter nal Application No
PCT/FR 97/00203

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 533267 A		ZA 9207106 A	17-03-94
EP 533268 A	24-03-93	AP 303 A	28-01-94
		AU 656021 B	19-01-95
		AU 2453092 A	25-03-93
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WO 9415920 A	21-07-94	AU 5815594 A	15-08-94
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WO 9504729 A	16-02-95	EP 0712397 A	22-05-96
		JP 9501171 T	04-02-97
WO 9506044 A	02-03-95	EP 0714389 A	05-06-96

RAPPORT DE RECHERCHE INTERNATIONALE

Dem Internationale No
PCT/FR 97/00203

A. CLASSEMENT DE L'OBJET DE LA DEMANDE
CIB 6 C07D295/20 C07D295/22 C07D211/32 C07D211/16

Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB

B. DOMAINES SUR LESQUELS LA RECHERCHE A PORTE

Documentation minimale consultée (système de classification suivi des symboles de classement)
CIB 6 C07D

Documentation consultée autre que la documentation minimale dans la mesure où ces documents relèvent des domaines sur lesquels a porté la recherche

Base de données électronique consultée au cours de la recherche internationale (nom de la base de données, et si cela est réalisable, termes de recherche utilisés)

C. DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie *	Identification des documents cités, avec, le cas échéant, l'indication des passages pertinents	no. des revendications visées
A	WO 96 02525 A (PIERRE FABRE MEDICAMENT) 1 Février 1996 voir le document en entier	1-19
A	EP 0 524 146 A (CIBA-GEIGY AG) 20 Janvier 1993 voir page 25 - page 29; revendications	1-19
A	EP 0 606 824 A (CIBA-GEIGY AG) 20 Juillet 1994 voir page 21 - page 26; revendications	1-19
A	EP 0 533 266 A (GLAXO GROUP LIMITED) 24 Mars 1993 cité dans la demande voir page 36 - page 42; revendications	1-19

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[X] Voir la suite du cadre C pour la fin de la liste des documents

[X] Les documents de familles de brevets sont indiqués en annexe

* Catégories spéciales de documents cités:

"A" document définissant l'état général de la technique, non considéré comme particulièrement pertinent

"E" document antérieur, mais publié à la date de dépôt international ou après cette date

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"O" document se référant à une divulgation orale, à un usage, à une exposition ou tous autres moyens

"P" document publié avant la date de dépôt international, mais postérieurement à la date de priorité revendiquée

"T" document ultérieur publié après la date de dépôt international ou la date de priorité et n'appartenant pas à l'état de la technique pertinent, mais cité pour comprendre le principe ou la théorie constituant la base de l'invention

"X" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme nouvelle ou comme impliquant une activité inventive par rapport au document considéré isolément

"Y" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme impliquant une activité inventive lorsque le document est associé à un ou plusieurs autres documents de même nature, cette combinaison étant évidente pour une personne du métier

"&" document qui fait partie de la même famille de brevets

Date à laquelle la recherche internationale a été effectivement achevée	Date d'expédition du présent rapport de recherche internationale
12 Mai 1997	21.05.97

Nom et adresse postale de l'administration chargée de la recherche internationale	Fonctionnaire autorisé
Office Européen des Brevets, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tél. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Luyten, H

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RAPPORT DE RECHERCHE INTERNATIONALE

Demande Internationale No
PCT/FR 97/00203

C.(suite) DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie *	Identification des documents cités, avec, le cas échéant, l'indication des passages pertinents	no. des revendications visées
A	EP 0 533 267 A (GLAXO GROUP LIMITED) 24 Mars 1993 cité dans la demande voir page 31 - page 35; revendications ---	1-19
A	EP 0 533 268 A (GLAXO GROUP LIMITED) 24 Mars 1993 cité dans la demande voir page 33 - page 38; revendications ---	1-19
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A	WO 95 06044 A (SMITH KLINE BEECHAM) 2 Mars 1995 voir page 16 - page 20; revendications -----	1-19

... feuillet (juillet 1992)

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